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American Heart Journal

VOL. 49 MARCH, 1955 NO. 3

Original Communications

THE ELECTROCARDIOGRAPHIC SPATIAL MAGNITUDE CURVE IN MAN

B. McA. SAYERS, M.Sc.,* F. G. SILBERBERG, M.B., B.S.,** AND D. F. DURIE, B.A.

MELBOURNE, AUSTRALIA

RECENT electrocardiographic studies have focused interest on the properties of the "ventricular gradient"[1] which is the name given to that quantity representing the integral (or area) of the magnitude-time curve of electrical potential over the QRS and T interval taking account of algebraic sign. It has been claimed that some diagnostic information, which is normally sought from linear electrocardiograms, may be obtained from a study of this quantity. If this claim is correct, then further useful information may accrue from a study of the magnitude-time curve of the spatial electrocardiogram. This magnitude-time curve is the time curve of the magnitude of the spatial "vector" representing the manifest cardiac dipole without reference to direction.

A study of the magnitude of the spatial "vector" is presented here, with some investigation of the spatial "ventricular gradient."

This study has been based on the hypothesis that the human heart may be considered to act as a small electrical dipole in a poorly conducting (electrical) medium, believed to be largely homogeneous. Although some workers do not accept this belief,[2] previous work[3] indicates that the hypothesis may be upheld with fair accuracy.

It is to be noted that the electrocardiographic records obtained are not in direct proportion to the total electrical activity of the heart, but only to the residual unbalanced currents of the heart within the body. The large mass of the heart has numerous sets of currents flowing in it due to a multi-path spread of the depolarization wave, and some of these currents must appear to cancel out when "viewed" from a distance. The degree of cancellation will depend both on direction and location, as well as magnitude, of the various currents flowing and will vary with time.

From the Baker Medical Research Institute and Clinical Research Unit, Alfred Hospital, Melbourne, Australia.

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*Present address: Imperial College of Science and Technology, London, England.

**R. B. McComas Memorial Research Fellow (1953).

If the potentials recorded on the body surface are derived from unbalanced residual currents, the electrocardiogram cannot correlate completely with the electrical events of the heart.

On this hypothesis, the magnitude of the recorded "spatial vector" is believed to be related to the resultant current flowing in the equivalent cardiac dipole. Such an equivalent dipole would establish a field, setting up currents which give rise to the observed potential distribution.

A study of the three dimensional magnitude M(t) of the equivalent cardiac vector as a function of time has been made, in each of 95 cases, according to equation (1) and the time-integral of this quantity for the QRS phase of the electrocardiogram determined.

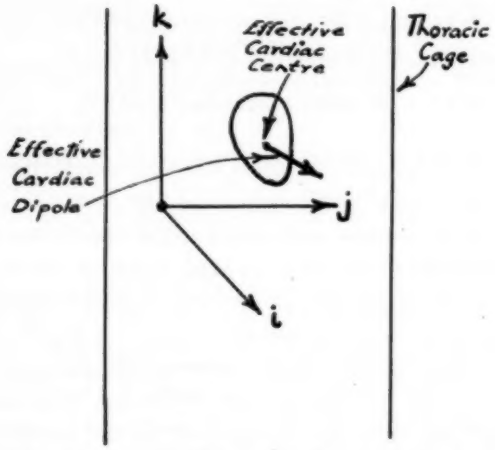

Fig. 1.—Rectangular axes *i*, *j*, *k*, in relation to body structures.

Let $X_{ijk}(t)$ be the projections on the three spatial rectangular axes *i*, *j*, *k* in the body of the "equivalent cardiac dipole" X(t) (Fig. 1), then

$$M(t) = \sqrt{\left\{ \Sigma_{ijk} \left[X_i (t) \right]^2 \right\}} \qquad (1)$$

METHOD

Vectorelectrocardiograms (102) of ninety-five patients were obtained using the system of Duchosal and Sulzer. Simultaneous loops in two planes were used to compute the instantaneous magnitude of the "dipole" current-time curve. Between 20 and 40 equally spaced time intervals over the duration of the QRS complex were employed for calculating the spatial magnitude-time curve. Special care was taken to insure that the loops of each pair of rectangular planes were assessed at the same relative phase.

In order to obtain their ventricular gradient the areas under the curves were measured by means of an Amsler Compensating Planimeter.

The cases (95) studied were classified clinically as thirteen normal, forty-two myocardial infarction, and forty other abnormals.

The majority of cases presented were studied in the course of routine investigations. The balance of the cases calculated have been obtained from papers by Grishman and Scherlis[4] and are reported by the kind permission of those authors.

The cases classified as normal have been free from any symptoms or history of cardiovascular disease.

The electrocardiographic classification of abnormalities is based on that employed by Wilson and associates,[5] and wherever possible have been substantiated by clinical symptoms, as for instance in cases of myocardial infarction. In each case of myocardial infarction there were a typical clinical history and course of infarction, and all records used were obtained in the "healed" stage except those otherwise marked. Some cases of clinical cardiovascular and electrocardiographic cardiac abnormality not readily classified have been included. A few patients with myocardial infarction were followed during their healing phases.

Note on Wave Shapes.—It was found to be difficult to determine the difference between what is commonly referred to as an S-T nonzero segment and what is considered an extension or irregularity superimposed on a QRS complex.

The simplest criterion for distinguishing between these two phenomena is the speed of "writing" the loop. A terminal irregularity having a speed not less than one-half that of the mean QRS loop is considered to be essentially part of a QRS loop. An irregularity having a speed less than one-fifth that of the mean QRS loop is held to be clearly an S-T or T-wave segment. None of the present curves were unclassified by this distinction.

For convenience in studying only the QRS complex without the T wave, we have introduced the concept of the form-factor. The form-factor is defined as the ratio of the area under the QRS curve to that of the smallest rectangular wave which completely encloses it.

Note on Frequency Response.—Most linear electrocardiograms are recorded on the basis that electrical components of frequency greater than 78 c.p.s. are largely eliminated. Even in conventional vector electrocardiography it has often been found necessary to utilize a drop in frequency response above 50 c.p.s. of at least 1.5 decibels per octave.[6]

However, since the duration of the QRS complex of the human electrocardiogram is approximately 80 milliseconds, the fundamental component of the electrocardiogram occurs at approximately 12 c.p.s. To allow a minimum of 10 harmonics, a frequency of 132 c.p.s. should be recorded at the same level of amplification as the fundamental 12 c.p.s.

Closer investigation shows components of appreciable magnitude at approximately 6 k.c.p.s. in some cases.[7] Rise times (involving 40 per cent of the maximum height of the curve) of 1.5 millisecond are often observed. Such rise times correspond to a 670 c.p.s. fundamental wave.

Thus, since all of the present series of curves have been calculated from the curves taken from a vectorcardiogram with characteristics as previously mentioned, only some of the higher frequency irregularities are shown.

OBSERVATIONS

1. *Shapes of Curves.*—Five types of curves were observed in the 102 tracings studied.

A. Smooth curves with no appreciable irregularity (36 cases): (1) symmetrical (20); (2) asymmetrical (16).

B. Double peak curves (22 cases): (1) first peak larger than second peak (15); (2) second peak larger than first peak (7).

C. Triple peak curves (7 cases).

D. Curves having irregularities, but not of sufficient magnitude to result in a well-defined peak (31 cases, Fig. 4, *A*).

E. Curves showing a S-T segment not at zero potential (6 cases). In these the junction (J) of the QRS and T is displaced (Fig. 4, *B*).

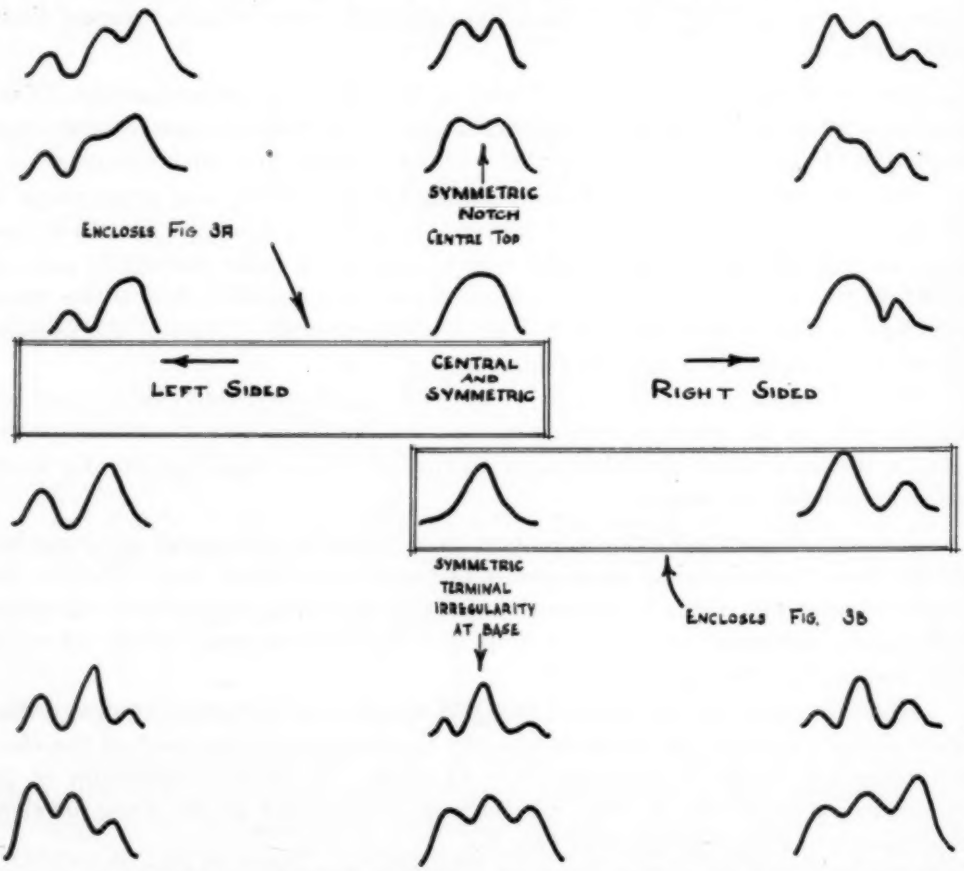

Fig. 2.—Graded sequence of curve; shapes showing some typical curves and their relative positions.

2. *Gradation of Curves.*—In a search for uniformity in the 102 electrocardiograms from the 95 cases studied, it was found that, apart from the general structural grouping described previously, no rigid classification was possible. Because of the difficulty of assigning any particular curve to any one of a set of possible groupings, it was realized that the curves formed a continuous sequence within a two-dimensional structure. An even gradation, from one curve

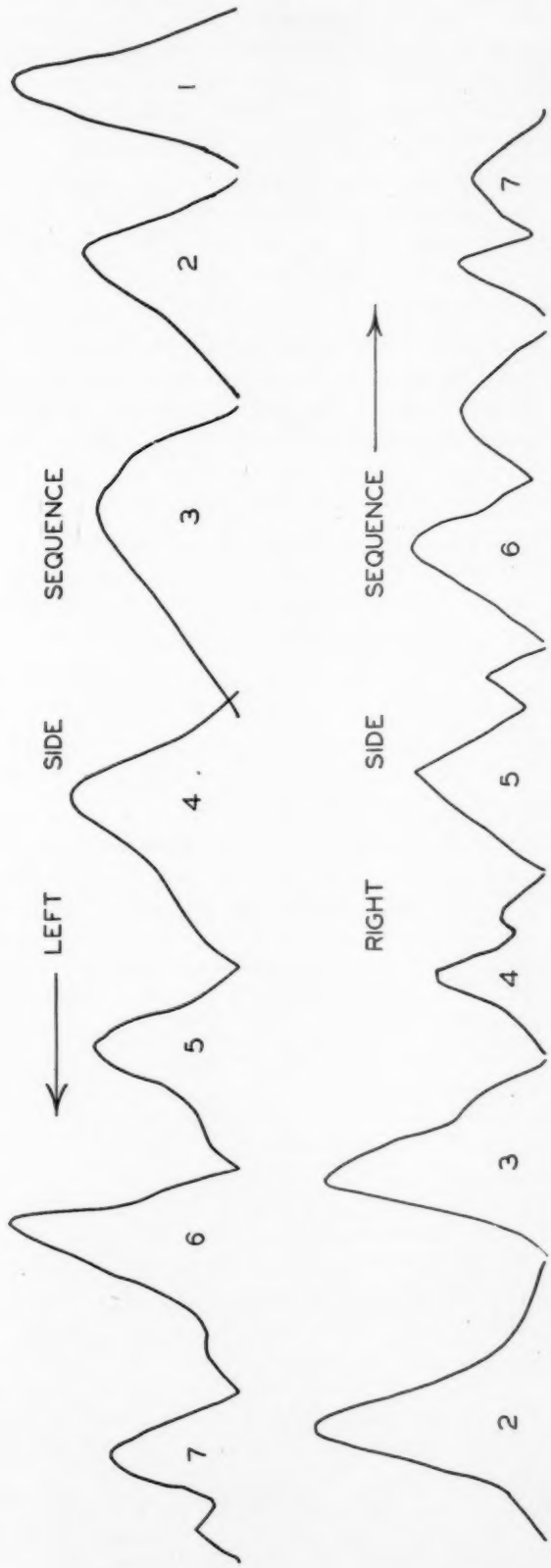

Fig. 3.—Two horizontal sections through the sequence of Fig. 2, showing a left-sided sequence and a right-sided sequence at a slightly different level.

of extreme irregularity (say predominantly left-sided) through a symmetric central curve to a curve of extreme irregularity which was a mirror image (predominantly right-sided) of the starting curve, was observed. Parallel sequences of graduated curves are readily seen. These move through generic central symmetrical curves which also form a graduated sequence.

Thus, referring to the diagrams of Fig. 2, the central symmetric curve resembles a half-rectified sine wave. Moving downward the symmetric curves show a flattening near the curve ends which eventually gives rise to a triple peak curve with the peaks at the ends subsidiary to the peak at the center of the curve. Moving upward from the central curve the symmetic curves show a flattening of the top which gives rise to a dip at the center (double peak) and thence to a further irregularity near the center leading to a triple peak curve with the central peak subsidiary to the end peaks. Moving horizontally away from the central peak curve in either direction leads to curves with mainly left- or right-sided irregularities. The form-factor decreases in both directions in moving away from the center. Fig. 3 illustrates the horizontal sequence.

The majority of places in the sequence have been filled by the curves observed in the present series. A few places are incomplete, but the sequence is clearly set out by the few typical curves shown. The fact that the difference between any two curves is in degree rather than in type is clearly demonstrated.

3. *Form-Factors.*—Normal cases showed a mean form-factor of 0.48. In the sequence of curves described, the form-factor decreases in both directions on either side of center. There is a clearly marked and significant variation in the form-factors between the symmetrical and asymmetrical curves of Group A.

Curves from recent myocardial infarctions show a significantly lower form-factor than those from healed infarcts. As the time since occurrence of infarct increases, the form-factor appears to rise steadily towards the value in the normal or the healed state. This is illustrated in the following Tables I and II.

TABLE I. EFFECT OF INFARCTION ON FORM-FACTOR

RECENT INFARCTS	HEALED INFARCTS
Mean of Form-Factors 0.42	Mean of Form-Factors 0.50

t—test: degrees of freedom, 22. t = 4.2: significant.

TABLE II. PROGRESS OF FORM-FACTORS IN FOUR CASES OF INFARCTION

CASE	AS FIRST OBSERVED AFTER INFARCTION (DURING EARLY HOURS OR DAYS)	AS OBSERVED AFTER EARLY HEALING (LATE MONTHS)
1	0.40	0.45
2	0.36	0.41
3	0.44	0.48
4	0.44	0.51

Several curves have been followed during the healing phase of infarction. An interesting feature in most of the cases is that the abnormal curves seen shortly after infarction give way to nearly normal curves after some weeks and then again show increasing abnormality approaching the final healed infarction form. As the earliest observation was at 12 hours after infarction and the early fluctuations in form-factor are not known, the reason that not all of the cases of infarction showed a clear return to near-normal curves before assuming the final abnormality representative of the healed infarct is probably that not all the cases could be studied at similar intervals.

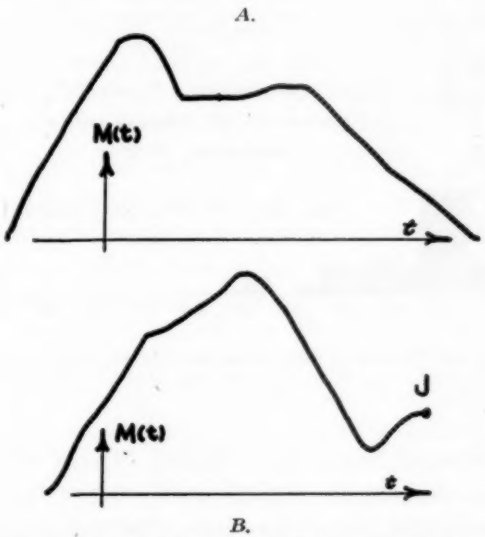

Fig. 4.—*A*, Typical curve with irregularity of insufficient magnitude to constitute a double peak. *B*, Typical curve showing a displaced QRS-T junction.

4. *Double Peak Curves.*—There was no correlation (29 cases) between the heights of the first or second peaks and the height of the enclosed minimum above the base line. However, when times of occurrence expressed as per cents of the total QRS duration were considered, the following feature was observed. There was a definite correlation between the time of occurrence of the first peak and both the time of occurrence of the second peak ($r = 0.62$) and the time of the minimum between the peaks ($r = 0.79$). The time of occurrence of the minimum and hence the time elapsed after the first peak is a linear function of the time-location of the first peak. The t-values calculated from the correlation coefficients were highly significant. Thus the duration of the "missing segment" between the two peaks is a function of, and hence apparently determined by, the time location of the start of the missing segment.

There appeared to be no relation between heights of either peak or of the minimum and the time location of occurrence.

5. *Curves Showing Irregularities.*—In this work (92 cases) irregularities are invariably considered to result in "missing segments" which have been subtracted from the equivalent smooth curve which just embraces all peaks. This was established as a convenient convention.

There appears to be a linear relation between the time of first occurrence of the first irregularity (i.e., of the time location of the starting point of the first irregularity) and the time location of the maximum change (curve minimum) when both are expressed as per cents of the total QRS duration. The distribution curve of the times of first appearance of the first irregularity is skew. The majority of cases fall within 5 to 15 per cent of the total QRS duration (Fig. 5). The distribution curve of the times of maximum change is more evenly distributed, with a shallow maximum toward 50 per cent of the QRS duration. This is a consequence of the linear relation expressed previously.

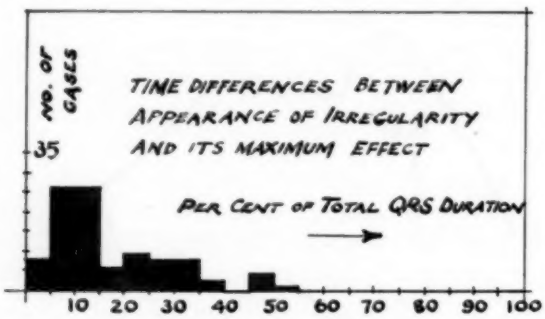
NO. OF CASES
TIME DIFFERENCES BETWEEN APPEARANCE OF IRREGULARITY AND ITS MAXIMUM EFFECT
35
PER CENT OF TOTAL QRS DURATION
10 20 30 40 50 60 70 80 90 100

Fig. 5.—Frequency distribution of time durations of irregularities from appearance to maximum effect (expressed as a per cent of total QRS duration).

6. *Correlation Between Shape and Clinical State.*—All definite double and triple peak curves are abnormal. Double peak curves are scattered among all clinical abnormal conditions that have been observed, being commonly found in cases of "bundle branch block." Bizarre triple peak curves are often found in cases of myocardial infarction.

Thus some curves may be classified as abnormal on inspection. However, some smooth curves, both symmetrical and asymmetrical, are found in cases clinically abnormal. Clinically abnormal curves do not generally fall into clinically classifiable groups. Normal cases have generally produced smooth but asymmetric curves.

Thirteen cases of left bundle branch block have been encountered. Of these seven showed definite double peak curves (second peak subsidiary) and six showed curves with nonzero and rising segments (Fig. 4, *B*).

In considering cases of left ventricular hypertrophy (fourteen cases), eight are smooth symmetric with large form-factors and six exhibit irregularities: Two predominantly left-sided and four right-sided, including one double peak curve.

One case (Grishman) was believed to have been left ventricular hypertrophy changing spontaneously to left bundle branch block. The original curve was smooth symmetric, and the left bundle branch block curve was a double peak similar to other curves of left bundle branch block.

Healed myocardial infarcts frequently exhibit left-sided irregularities. Several are largely smooth curves and several bizarre triple peak and right-sided curves.

DISCUSSION

1. *Method.*—The geometrical system of electrode placement used corresponds with that of Duchosal and Sulzer. In common with other systems, this is not completely reliable but it is difficult to see how to devise a more reliable system. The reason for the lack of reliability concerns the field structure due to the cardiac dipole in the presence of slight inhomogeneity.[3] As a result, this system is to be considered as a transformation upon the information available and is most suitable for use as a base for experiment rather than for diagnostic purposes.

The limit to the high-frequency response plays a significant part in this work. A paper in preparation[7] describes the use of high-frequency components as a guide to impedance variations in the heart as an electrical generator. The absence of high-frequency components in the electrocardiograms here discussed permits only some basic electrical patterns to be studied.

2. *The Ventricular Gradient.*—The ventricular gradient has not been explicitly studied in this work for two main reasons. First, despite common usage, ventricular gradient is not a vector quantity. It is immaterial whether the fundamental electrocardiographic quantity is chosen as potential or current. Hence "direction" is not an inherent property of the ventricular gradient. Since this is contrary to present usage, a major difference in point of view is evident.

Secondly, while it has been claimed that the ventricular gradient is a measure of the duration of the excited state,[1] this is not so. Such a belief could only be tenable if both polarization and depolarization processes are comparable, i.e., from the same type of source, similar in both location and process. However, in a previous paper[3] it has been shown that the process responsible for the generation of the QRS component is of a type quite different from the process responsible for the T component. Hence, such a concept as that of the duration of the excited state (with both QRS and T waves considered) is meaningless, and the application confusing.

For these reasons it has not seemed rational to consider QRS and T wave components of the electrocardiogram together, since only confusion could result. When it can be determined how much of the T wave is due to a process similar to that of the QRS wave, and how much to dissimilar processes, it will become possible to consider QRS and T-wave processes together.

The alternative to using the ventricular gradient has been the study of the form-factor of the QRS wave.

3. *The Form-Factor.*—No measurement of total QRS or QRS-T duration has been made in this investigation (except in the calculation of the form-factor) for the reason that to do so would further complicate a preliminary investigation as previously described.

However, in order to include the total duration in the information and to assess curve shape, the concept of the form-factor was introduced. For curves of equal duration, the magnitude of the factor gives a measure of the approach of the curves to a condition in which the product of the total instantaneous positive charge by the dipole spacing between the "centers of gravity" of positively and negatively charged segments is constant over the QRS period.

This constancy of the dipole moment, however, is not closely realizable in practice. The choice of square-wave comparison was made for convenience and with a mind to the ideal characteristics for a flat strip of muscle.

It may be shown that the equivalent dipole moment curve of such a flat strip excited at constant velocity by a wave of excitation having a straight leading edge has the form of a triangular wave with a rapid uprise and a slow but straight line decay. When account is taken of the extension to an idealized heart in a homogeneous medium, the dipole moment curve takes the form of a trapezoidal wave with very sharp leading and trailing edges and a shallow peak at near 50 per cent of the total QRS duration. The further idealization to a square wave is evident.

The dipole moment expression for a flat strip of constant charge density (d) in the polarized zone, of length (l) width (b) and constant velocity of the wave of excitation (v) is given by

$$M = (k_1 l^2 - k_2 l v t) b d$$

for which k_1 and k_2 are constants, t is time, and the expression is valid only for the period after the start of the wave of depolarization. It will be evident that the dimensions of the muscle strip, the charge density, and the velocity of the wave of depolarization all play a part in determining the instantaneous value of the dipole moment.

Hence, variations in any of these components will generally produce changes in the form-factor. Granted that the charge density be held constant throughout, variations in the form-factor from the normal range due to a given muscle segment may be due to changes in the dimensions of the segment concerned (i.e., in path contour of the wave of depolarization) and in the velocity of local propagation of the wave. The greater the variations, the more the irregularities in dipole moment, and probably the greater the change in the form-factor. Thus the magnitude of variations from normal of the form-factor gives an indication of the presence and magnitude of variations in progression and contour of the wave of excitation through the heart muscle.

Generally it has been found that the form-factors for abnormal curves are within or without the range of values found for normal curves. Insufficient cases of most types of lesions make generalization difficult. However, certain notable features exist.

First, early stages of myocardial infarction showed significantly lower value of form-factor than that in normal individuals or in later stage infarctions. Evidently considerable variations in path contour and progression were present. These showed a tendency to rearrangement as healing progressed and the form-factor increased toward normal. This lowering of the form-factor was found in all cases of recent myocardial infarction seen; hence, it is not likely to be entirely due to the actual necrosis present because of the wide variation in the site of infarct. It is probable that the effect is related to the recognized irritability of recently infarcted and contiguous areas.

Secondly, smooth symmetrical curves, mainly cases of left ventricular hypertrophy, showed a higher value of form-factor than the normal. In the presence

of clinically appreciable left ventricular hypertrophy, the effect of path contour and progression variations should be less marked, due to the larger spacing of the electrical centers of gravity with the electrically important left ventricle enlarged.

The cases of left bundle branch block showed form-factors of some considerable spread, but insufficient cases have been seen to permit determination of the significance of the displacement of the mean from normal.

Generally, it is suggested that the decrease in form-factor expected with the extension of the QRS duration appears to be present. It is evident that some rearrangement of the pattern contour and velocity of local propagation is present, and furthermore the degree of modification of these varies from case to case. There can be no doubt that an otherwise normal heart could simulate a case of left bundle branch block by means of localized electrical variations. However, so far as is known such changes are only produced by pathologic lesions, which could be of many different types. In view of the scatter of curves seen it is probable that many different lesions do produce the pattern of left bundle branch block.

4. *Curve Types and Grouping.*—Two points of view have been considered. First, it is suggested that there is some evidence to justify classification of curves into groups on the basis of shape (not according to general characteristics such as has been done in the section on results). This evidence may be summarized thus: the form-factor shows a significant difference between smooth curves of the symmetric and asymmetric types. Furthermore, the form-factor appears to be related to the stage of healing in infarction. Left-sided and right-sided irregularities have been found, and curves of similar shape appear throughout the series. However, any attempt to classify curves by shape is defeated by the difficulty of determining lines of demarkation and of allotting boundary cases. The fact that the electrical activity recorded by the electrocardiogram is related, not to the total cardiac electrical activity but only to the resultant activity from innumerable resultant currents, also points away from a groupwise classification.

The second approach to the problem involves the continuously graded sequence of curves. In the present study such a graded sequence has been found to fit the facts closely. There is good reason why this should be so.

From the point of view of electrical activity, differing electrocardiograms may be the result of differences in (1) conductivity and homogeneity of the external medium; (2) ability of segments of resting cardiac muscle to alter their states of polarization (e.g., in the presence of electrolyte unbalance, muscle death, or ischemic disease); (3) speed of conduction of depolarizing wave across various paths (e.g., bundle branch blockage has been suggested to cause an intermittent change in the speed of the wave through the ventricular bundles); (4) path lengths and contours along which the activating wave must pass.

Alterations in any of these four ways may give rise to very similar electrical effects, but it is evident that they describe the results of a wide variety of cardiac abnormalities.

Hence, differentiation into groups of curves according to clinical or physical abnormality cannot reasonably be expected to agree generally with a differen-

tiation according to observations of resultant unbalanced electrical activity, nor likewise will the position of the curve within the sequence of Fig. 2.

The fact of a continuously graded sequence of all the cases seen is of great importance. Evidently, the electrocardiograms due to various pathologic lesions may be of the same general type. Differentiation on the basis of the shape of the spatial magnitude curve is virtually impossible. More important still, it is evidently impossible to classify curve types when such a continuous gradation is present. This throws doubt on the validity of differentiating curve tendencies in the vectorelectrocardiogram.

5. *Myocardial Infarction and Other Lesions.*—Interpretation of changes in any electrocardiogram, as a result of pathologic lesions, is difficult for several reasons.

Goldberger and Eyster[8] have shown that the ventricular surface of the turtle heart is characterized by a field "map" showing simultaneous appearances of electrical "sources" and "sinks" (maximum positive and negative regions) which show growth and decay and changes in orientation. Hill[2] has shown similar effects on the human chest surface. Mauro and associates[9] and Nahum and associates[10] have verified and extended these findings. The effect of infarct or other injury must be related to its location with respect to such "poles" of activity. Hence, the magnitude of the change due to a pathologic lesion will not be related directly either to the extent or location of the injury, since numerous poles are known to be present simultaneously under some circumstances.

Another effect is also believed to play a part in the electrical changes of a given lesion. The path of depolarization stimuli over a small region can and will be tortuous and approach other path contours. When the waves travel along both path contours simultaneously, and approach one another, a relatively large area of muscle will be stimulated simultaneously. This will give rise to a "pulse" of current of quite short rise time in the electrocardiogram. Injuries in such areas give rise to very large effects. This phenomenon has been verified both in human beings and animals by Sayers and Silberberg,[7] using a high-frequency apparatus. Observations on the phase of large (high-frequency component) changes may provide a means for identifying the location of lesions. Taken in conjunction with the large change of form-factor in early myocardial infarction, this may be a useful experimental method. It will be noticed that some agreement with the zonal interference theory is suggested by this work.

SUMMARY AND CONCLUSION

1. A new transformation method for studying the cardiac electrical activity is described. This consists of the calculation of the total resultant spatial magnitude of the equivalent cardiac vector as a function of time; 95 human cases have been studied.

2. The concept of form-factor of such curves has been defined and it is shown that the form-factor gives some indication of variations in contour and progression of the wave of stimulation throughout the heart.

3. The existence of irregularities in many abnormal cases and determining relations of the irregularities have been demonstrated and discussed.

4. It is shown that all the tracings studied (102) fit only into a continuously graded two-dimensional sequence and that many types of abnormality have curves scattered throughout the sequences.

5. The notion of ventricular gradient is briefly discussed, and reasons are given why the consideration of QRS and T-wave components together is unsatisfactory and confusing. It is concluded that the use of the form-factor is less likely to cause confusion.

6. Evidence suggests that high-frequency components of the spatial magnitude vectorelectrocardiogram may be of considerable significance.

7. Cases of left bundle branch block are shown to have a common curve shape. A difference in curve shape between cases of left bundle branch block and left ventricular hypertrophy has been suggested.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Nos presenta pro le studio del activitate electrocardiac un nove methodo de transformation que consiste in calcular le resultante magnitude spatial total del equivalente vector cardiac como function del tempore. Le methodo esseva applicate a 95 casos human.

Le concepto del "factor de forma" in tal curvas es definite. Il es demonstrate que le factor de forma indica in un certe mesura le variationes de contorno a del progression del unda de stimulation a transverso le corde.

Es discutite brevemente le concepto del "gradiente ventricular." Es explicate alicunes del rationes pro que le consideration combinate del componentes QRS e T resulta in un confusion que pote esser evitate per substituer le uso del factor de forma.

Es presentate datos in supporto del conclusion que le componentes a alte frequentias del vectocardiogramma a magnitude spatial es possibilemente de grande importantia.

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A SPATIAL MAGNITUDE ELECTROCARDIOGRAPH

B. McA. Sayers, M.Sc.*

Melbourne, Australia

THE application of the concept of the spatial magnitude of the cardiac equivalent vector has been studied in a preliminary report on 100 human beings.[1] In view of the time-consuming procedure required to calculate the spatial magnitude curve as a function of time, it has been found advisable to develop automatic equipment to provide the results directly. This paper describes the equipment currently in use for this purpose.

By way of introduction it may be pointed out that linear or scalar electrocardiographic techniques record the component magnitude of the cardiac potentials between a pair of electrodes as a function of time. The vector presentation records the magnitude of the cardiac potentials in each of three rectangular planes as a function of direction, and only incidentally of time (by means of time markers). The present technique of spatial magnitude electrocardiography records the magnitude in space of the equivalent cardiac vector as a function of time.

It is generally considered that the quantity recorded in the electrocardiograph (ECG) is potential. However, it has been shown in this laboratory (unpublished) that there is a finite value of the resistive component of the internal source impedance of the body as a (cardiac) potential generator. (The technique of this measurement is indicated in addendum to a paper by Sayers.[2]) In other words as an appreciable current flow through the body tissues may be demonstrated, the recorded potential may be considered as an ohmic voltage drop through a dissipative medium; while the quantity being recorded is potential, the fundamental quantity is current. The applicability of this concept is seen when the quantity, "ventricular gradient", is being considered. There is some evidence that this quantity is significant. However, the dimension[3] of ventricular gradient is potential-time (e.g., volt-second) which is not that of any common significant unit.[4] If the fundamental quantity is considered to be "current", the dimension of ventricular gradient becomes current-time (e.g., ampere-second), which is that of "charge". Thus on this hypothesis, ventricular gradient has some physical meaning as related to the total unbalanced charge established upon the body structure as a result of the heartbeat. It is evident that this can have no significance unless the total net electrical activity of each beat

From Baker Medical Research Institute and Clinical Research Unit, Alfred Hospital, Melbourne, Australia.

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*Present address: Imperial College of Science and Technology, London, England.

is being considered. Thus a further development of the spatial magnitude ECG is the integration, with respect to time, of the ECG signal, to produce the ventricular gradient. This is interesting both by reason of the simplicity of the representation and the implied physical relation between the ventricular gradient and the net charge produced on cardiac muscle cells. This representation, that the ECG is a measure of net current flowing between electrodes, has been adopted throughout this paper.

THE PROCESSES OF THE TRANSFORMATION

In considering three current components along rectangular axes *i*, *j*, *k*, on the human body

$$X_i(t) \qquad X_j(t) \qquad X_k(t)$$

evidently the spatial magnitude of the equivalent cardiac dipole is given by

$$M(t) = \sqrt{\left\{ \Sigma_{ijk} \left[X_i(t) \right]^2 \right\}}$$

The three components $X_i(t)$; $X_j(t)$; $X_k(t)$ thus selected are amplified, squared separately, and then added together. The square root of the resulting signal is then taken, and the resulting signal recorded and/or integrated as required. The process of obtaining the magnitude M(t) has been sectionalized into the specific mathematical processes for the present equipment (Fig. 1). The equipment units follow.

1. Preamplifier, three channels
2. Main amplifier, three channels
3. Squaring, three channels
4. Addition of three components
5. Square root
6. High pass filter
7. Integrator

CIRCUITRY

1. *Preamplifier.*—This follows the standard practice of having two push-pull input stages: high cathode impedance of the input pair with tube selection permits an in-phase rejection ratio of 1,200 to 1 or better.

2. *Main Amplifiers.*—Two push-pull stages with fine gain controls on each channel are used. Fine control for balancing is achieved by a variable resistance in the cathode circuit of the twin triode in series with the high tension supply to the push-pull pair (Fig. 2). Control of bias thus gives control of voltage drop across the series tube, and the gain in this stage varies proportionally. Control of gain in the range 40 to 100 per cent of maximum gain is practical with the advantage that the in-phase rejection ratio of this stage does not vary appreciably over the entire range of gain control. The main amplifier may thus be taken out and used separately as an input amplifier. Both the main amplifier (for the latter reason) and the preamplifier are battery driven, and a well regulated D. C. filament supply is used.

THE SQUARING CIRCUIT

This circuit makes use of the approximate multiplication law[8]

$$i_p = k_1 + k_2 e_g + k_3 (e_g)^2$$

when e_g is applied grid signal.

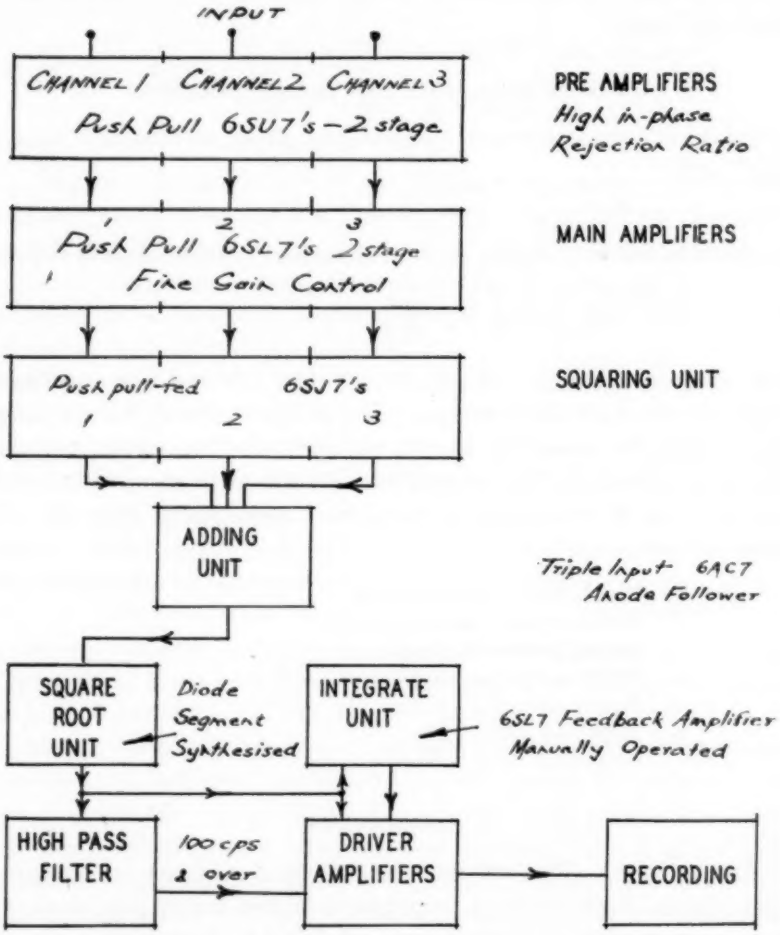

Fig. 1.—Block diagram of sectionalized processes used in calculating the spatial magnitude of the "cardiac vector."

With a fraction of e_g applied to the suppressor grid an improvement in form of the output is observed according to the approximate relationship

$$i_p = k \cdot e_{g1} \cdot e_{g3} \ *$$

provided that a pair of pentodes with a common load is used (driven push-pull to eliminate odd power terms). Then

$$i_p = k_1 + k_4 \cdot e_g^2$$

The circuit follows approximately that of Ross and Shuffrey[5] with the modification that a push-pull input is already available (Fig. 3). Testing is done with

*e_{g1} is signal on grid 1. e_{g3} is signal on grid 3.

a push-pull sinusoidal input signal based on the feature that

$$\mathrm{Sin}^2 wt = \tfrac{1}{2}(1 - \cos 2wt)$$

and if D.C. components may be neglected the output has the form of a double-frequency sine wave. Thus the setting of each channel for exact symmetry of double-frequency sine wave output simplifies the testing and balancing.

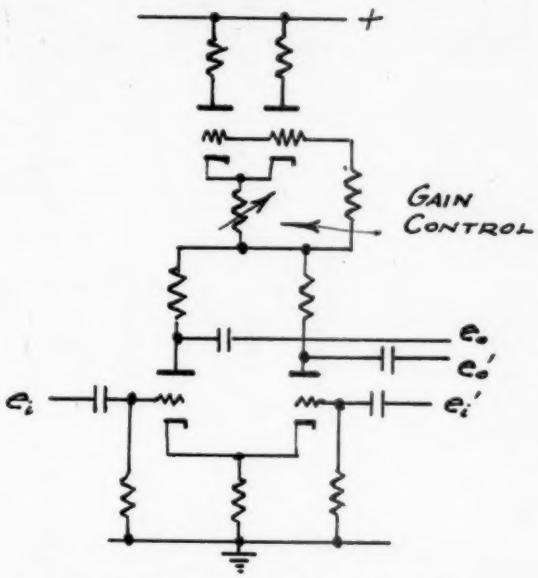

Fig. 2.—Fine gain control of push-pull stage.

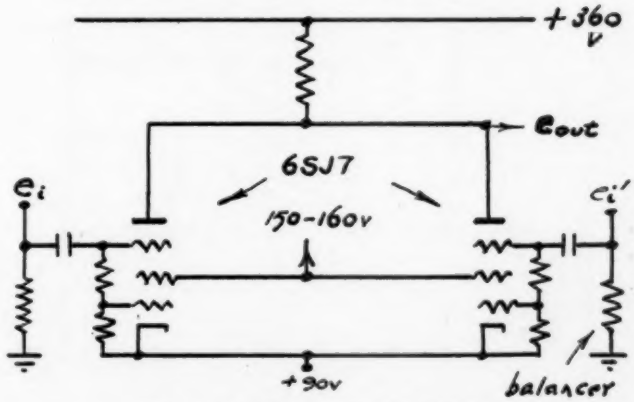

Fig. 3.—Push-pull squaring circuit.

This circuit requires careful isolation of input from the previous stage through good quality blocking condensers. If direct coupling is required, a high series impedance is necessary, due to the divider network between cathode, grid, and suppressor which is connected directly to the input. 20v RMS (square root of mean square) input may be handled up to a frequency of 10 k.c.p.s. The three components are added together in a triple input anode follower. The output from this circuit goes then to a high pass filter of the dual network feedback type and also to the square root taking circuit.

HIGH PASS FILTER

This consists of a bridged-T transmission filter with a null at 50 c.p.s. and a feedback circuit bridged-T filter with a null of 200 c.p.s. The combination of these two provides a sharp rise of output from about 100 c.p.s., a

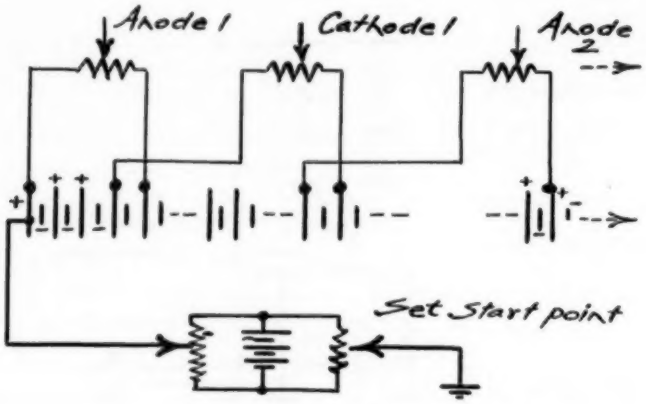

Fig. 4.—Circuit for diode segment potentials.

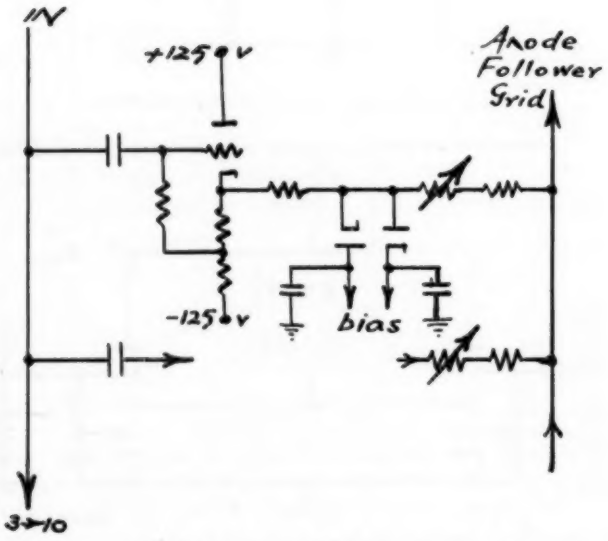

Fig. 5.—Multiple segmented diode square root circuit.

knee to the curve at 200 c.p.s., and approximately flat response beyond 300 c.p.s. The purpose of this circuit is to eliminate the fundamental beat and the first few harmonics so that the phase location and amplitude of high-frequency components may be more readily studied. It has been found that high-frequency components in the electrocardiogram are of considerable significance in following the effects of procedures which alter the "conductivity" of the "triggering impulse", or wave of depolarization.

SQUARE ROOT CIRCUIT

This circuit is based upon the fact that the conducting voltage segment of a duo-diode may be controlled by two bias potentials. The voltage width and voltage of start of the conducting segments of a series of diodes fed from cathode followers in parallel were made continuously variable (Figs. 4, 5 and 6). The output signals from these may be varied in gain (i.e., by varying the effective

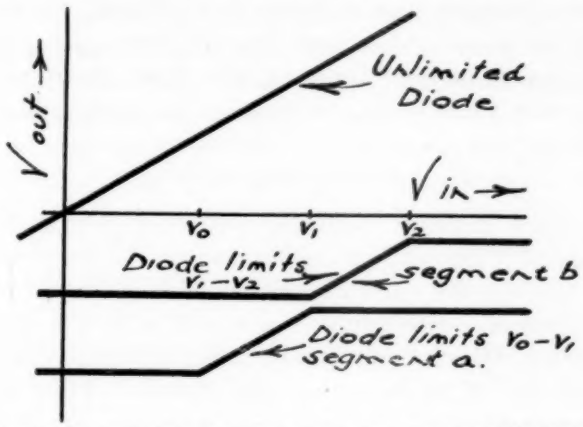

Fig. 6.—Showing the synthesis of square root curve from multiple diode segments.

slope of the conducting segment with an output potentiometer) and added together to produce an output curve of semiparabolic form under a steadily increasing output. Only one-half of the parabola is required since the input signal is the result of a squaring process and only goes one way, i.e., positive. Careful setting of the input zero level is required as small errors in this quantity can give rise to large output errors.

Satisfactory root-taking is possible at up to 50 volt input level. In this range, the higher the input RMS level the less will be the effect of errors in segments near zero.

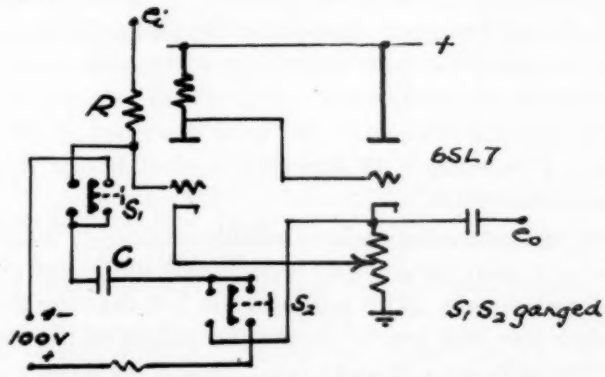

Fig. 7.—Manually controlled integration circuit.

INTEGRATING CIRCUIT

This has not been in regular use. The circuit is directly coupled to the square root taking circuit output and is operative for a duration dependent

upon a press button control (Fig. 7). Release of the press button causes the condenser to discharge to a known voltage level. In the present case the level is 100 volts, and it will be seen from the circuit that the output level before balancing is higher than the input level by 100 volts D.C. The circuit has been described by Gray[6] and Korn and Korn.[7] A strictly repetitive integration with automatic discharging and resetting of the integrating condenser is at present considered impracticable because of the variation in heart rate among human beings, and more so between human beings and animals, for both of which the present apparatus is in use. The resetting and discharging must be controlled from the starting point of the P wave, and at a fixed duration after this point. Variations in P waves and P-P intervals make this extremely difficult.

DRIVER AMPLIFIER

Driver amplifiers utilizing feedback-controlled gain and cathode-follower output permit spot shifting with an output voltage maximum of 170 volts peak-to-peak. Two channels are currently in use with a Cossor 1035 double-beam cathode-ray oscilloscope. Recording is achieved with a Southern Instruments continuous-recording camera using 70 mm. paper driven at from 10 to 15 in./sec. for human beings and 15 to 36 in./sec. for animals. Time marking uses a 50 c.p.s. calibration signal.

The over-all time constant of the apparatus is in the vicinity of 0.2 sec. as used at present, but up to 1 sec. is possible without modification. Approximately 10 k.c.p.s. is the upper limit frequency for flat response, mainly due to the frequency doubling effect of the squaring circuit.

DISCUSSION

A fundamental interest with equipment of this type concerns the average realization accuracy of the processes involved.

The processes of least accuracy are those of squaring, square rooting, and integration. The accuracy of squaring has been discussed in the original paper on the subject.[4] It has been our experience that adjustment of the apparatus is practicable to the point at which no error is perceptible when wave forms are studied with a cathode-ray oscilloscope.

The accuracy of integration has also been described in *Waveforms*[8] and by Korn and Korn.[7] Processing with an error level of better than 3 per cent of maximum signal is obtainable.

The accuracy of square-rooting is a variable quantity. Since a finite number of segments has been used, large input signals will suffer less percentage distortion than small input signals. This is due to the fact that the slope of the square root curve becomes less and less for increasing values of the input and may be approximated eventually by a straight line. Hence, for large values of the input the square root curve may be more readily approximated by few segments. Checks on the apparatus used indicate that, for a near maximum level input, the errors are in the vicinity of 7.5 to 10 per cent. Increasing the number of segments will reduce this error. For a signal with an input level in the vicinity of

5 to 10 per cent of maximum usable input level the errors are naturally considerable and adjustment of the input gain to near maximum usable level is necessary.

In considering over-all accuracy it is of prime importance to know the reliability and reproducibility of the experimental procedures. It is well known for instance that the attitude and respiration of a human subject play a large part in varying the form of any type of electrocardiogram from the subject. Some slight measure of variation can be obtained in the spatial magnitude electrocardiogram from a given subject from day to day even when all controllable factors have been standardized. In animal experimental work involving operative procedures much more variation is encountered.

In general, variations of the higher frequency ECG components, higher than 200 c.p.s., of up to 10 per cent in magnitude are seen in the human subject from day to day. Hence processing accuracies of better than 10 per cent error are generally of little importance. Checks against calculated spatial magnitude curves reveal an error of slightly more than this; most of the error arises in the present square root taking circuit.

For much experimental work only comparative measurements are taken, and the square root circuit is not used.

SUMMARY

Details of a spatial magnitude electrocardiograph, which plots the total effective magnitude of the equivalent cardiac dipole as a function of time, are presented. The processes of squaring, adding, square root taking, and integration are described, and the accuracy of the procedures briefly discussed.

SUMMARIO IN INTERLINGUA

Es presentate detalios de un electrocardiographo a magnitude spatial que es equipate a provider directemente le valores del magnitude efficace total del dipolo cardiac equivalente, exprimite como functiones del tempore. Isto evita le lente labor que es requirite pro establir le curva del magnitude spatial como function del tempore per medio de calculationes. Es describite le processos de quadrar, adder, extraher le radice quadrate, e integrar. Le exactitude del procedimentos es discutite brevemente.

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EVALUATION OF THE CALIBRATED DISPLACEMENT, VELOCITY, AND ACCELERATION BALLISTOCARDIOGRAPH IN ANGINA PECTORIS

J. E. Smith, M.D.,* Ludwig G. Lederer, Ph.D., M.D.,** and James C. Mandes, M.D.***

Washington, D.C.

THE diagnosis of typical angina pectoris as orginally described by Heberden is usually not difficult for the modern clinician and needs no description. Many difficulties in diagnosis do arise in atypical cases, and the clinician has long searched for objective methods of evaluating these cases. In order to develop thorough, objective studies, a series of twenty cases of angina pectoris has been studied, and evaluation of the objective findings has been attempted. These cases have been studied with resting electrocardiograms, exercise electrocardiograms, and with the calibrated bar-magnet ballistocardiograph that measures the displacement, velocity, and acceleration components of body motion, simultaneously. Thus, a reasonable attempt can be made to evaluate the sensitivity of each method as objective evidence of disease and may be valuable to the clinician in atypical and difficult diagnostic cases.

METHODS AND MATERIAL

The clinical material used was fifteen cases of typical angina pectoris in which the patients complained of a pressure-type substernal pain on exertion. In most instances, there was radiation to one or both arms. Five cases were atypical angina pectoris in which the clinician felt that the diagnosis was due to coronary heart disease, but in which the symptoms were such that objective methods of testing would be extremely valuable. These included cases in which the pain on exertion was located in the back or precordial area, or was substernal in location, had little relation to exertion, and was related more to emotional factors or occurred at rest. Since we were interested in evaluating the electrocardiogram with the ballistocardiogram, it was felt that this would be a biased sample for evaluating the electrocardiogram and exercise test in angina pectoris on a statistical basis, as our interest was in obtaining angina cases with normal

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*Assistant Clinical Professor of Medicine, George Washington University Medical School, and Chief, Medical Standards Branch, Civil Aeronautics Administration.

**Assistant Clinical Professor of Medicine, George Washington University Medical School.

***Resident Fellow in Cardiology, George Washington University Medical School.

electrocardiogram to evaluate with the ballistocardiograms. This type of case predominated in our referral cases for study.

It is our belief that the resting electrocardiogram in angina pectoris is so frequently normal or nonspecific as to be of limited objective value. The exercise electrocardiogram has been of value in these cases but was positive in only 50 per cent of our cases.

Electrocardiographic Data—Twenty Cases of Angina Pectoris.—These data included normal resting electrocardiograms in fourteen cases; borderline electrocardiograms in six cases; positive exercise tests in ten cases. The borderline electrocardiogram resting abnormality in these cases consisted of low-amplitude T waves in Leads I, aV_L, and V_4, V_5, and V_6. There were no abnormal Q waves and no inverted T waves over the left chest or Lead I. One case also had first degree A-V block with a P-R interval of 0.32 sec., but the electrocardiogram was otherwise normal. In none of these borderline cases could the resting electrocardiogram be considered diagnostic of coronary heart disease but could be considered as suspicious of coronary heart disease.

Ballistocardiographic Data—Twenty Cases of Angina Pectoris.—The techniques of measuring body motion as displacement, velocity, and acceleration with close approximation of the single degree of freedom concept have been published previously.[1,2] Comparison of abnormality is based on normal standards.[3] Displacement comparisons are made because of the familiarity of this type of measurement to the average clinician and the ease of utility of displacement readings. Also, the average clinician may experience great technical difficulties in using velocity and acceleration ballistocardiographs due to ambient vibration, interference from buildings, or other environmental factors. The instrumentation and recorder are calibrated so that one chart millimeter of amplitude equals 0.0002 inch displacement, 0.10 mm./sec. velocity, and 3.0 mm./sec.^{2} acceleration.

Displacement:

IJ segment = Mean = .0010 inch
= Standard Deviation = .0002 inch

Wave Ratio Measurements

Mean	Standard Deviation
Percentage HI of IJ	
63	11.5
Percentage JK of IJ	
130	25.0

Timing

	Mean	Standard Deviation
R-K	0.37	0.024
R-J	0.26	0.022
R-I	0.16	0.018
R-H	0.10	0.016

Velocity:

IJ segment = Mean = 0.85 mm./sec.
= Standard Deviation = 0.16 mm./sec.
JK segment = Mean = 1.00 mm./sec.
= Standard Deviation = 0.15 mm./sec.

Wave Ratio Measurements

Mean	Standard Deviation
Percentage HI of IJ	
82	17.7
Percentage JK of IJ	
118	12.0

Timing

	Mean	Standard Deviation
R-K	0.32	0.02
R-J	0.21	0.02
R-I	0.13	0.01
R-H	0.08	0.02

Timing: Peak of J to peak of K

0.11 0.01

Acceleration:

JK = peak of J to peak of K
JK segment = Mean = 36.5 mm./sec.^{2}
= Standard Deviation = 11.0 mm./sec.^{2}
Base line to K peak = Mean = 11.3 mm./sec.^{2}
= Standard Deviation = 2.8 mm./sec.^{2}

The comparison of displacement IJ amplitudes of twenty cases of angina pectoris and fifty normal subjects between the ages of 20 and 40 is illustrated in Fig. 1.

CASE REPORTS

CASE 1.—A 33-year-old male attorney. This case was the youngest of the series. He complained of severe pressure-type chest pain located deep in the chest and in the back between the shoulder blades. This pain was typical of angina due to coronary heart disease as it came on after exertion or excitement, lasting usually not more than a few minutes and relieved by rest and nitroglycerin. No arm pain was noted.

The patient came from a family of known cholesterol metabolism disorders with xanthomatosis. One sister had a coronary occlusion at age 29. Cholesterol blood studies in this patient have been consistently abnormally high. He had been told that he had angina pectoris on two previous examinations, but the electrocardiogram had been interpreted as normal in these examinations. There were no objective findings of heart disease.

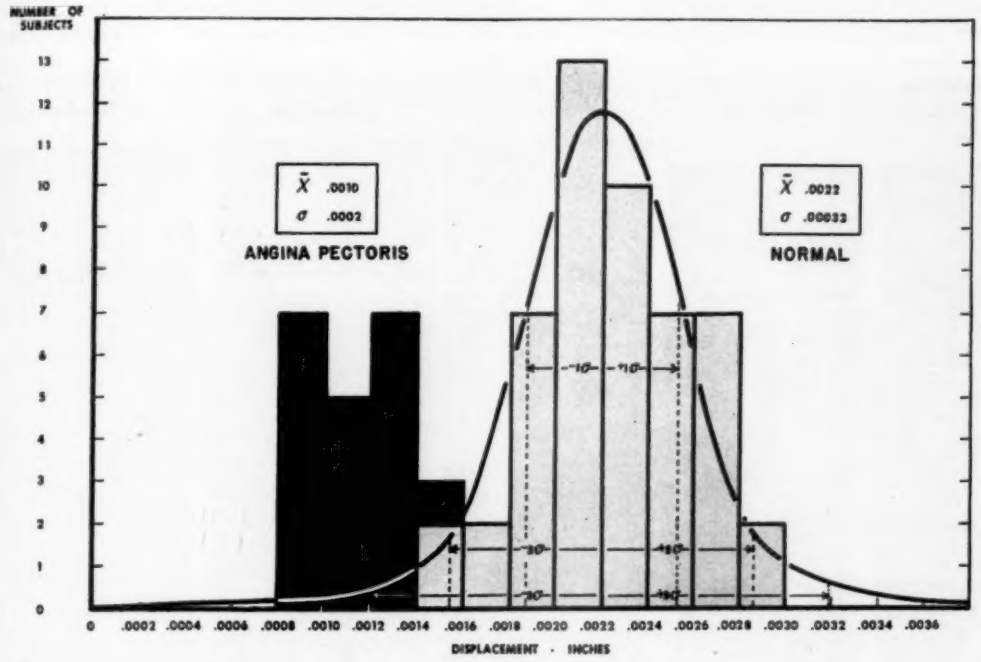


Fig. 1.—Comparison of the amplitudes of the displacement IJ segments in fifty normal subjects between 20 and 40 years of age and twenty cases of angina pectoris.

The resting electrocardiogram was normal. A double-exercise test was normal. The exercise test in this case is illustrated in Fig. 2. The ballistocardiogram shows low amplitudes on the displacement curve, IJ = 0.0012 inch. The acceleration curve shows changes usually found in coronary heart disease. The acceleration K peak is notched and 15 mm./sec.^{2} when measured from the base line. Note the extremely high-amplitude acceleration M waves which correspond in timing to the opening of the mitral valve. This may be graphic evidence that when the left ventricle fails to accelerate blood normally, it fills faster than it empties. At least the forces transmitted through the body frame are greater in early diastole than in systole. When the displacement curve is studied carefully, one would certainly experience great difficulty in predicting the corresponding acceleration curve from a purely mathematical orientation per se. The ballistocardiogram of this case is illustrated in Fig. 3.

CASE 2.—A 37-year-old male, formerly a professional athlete complained of bouts of severe substernal pain on exertion and excitement which lasted only a short time and responded to nitroglycerin. This man weighed 240 pounds and was of excellent muscular development and appeared to be in excellent health. He had these attacks of exertional chest pain for over three years, gradually increasing in severity. Blood pressure 138/76 mm. Hg. No murmurs or evidence of cardiac abnormality. The resting electrocardiogram was normal, and the double-exercise test was normal.

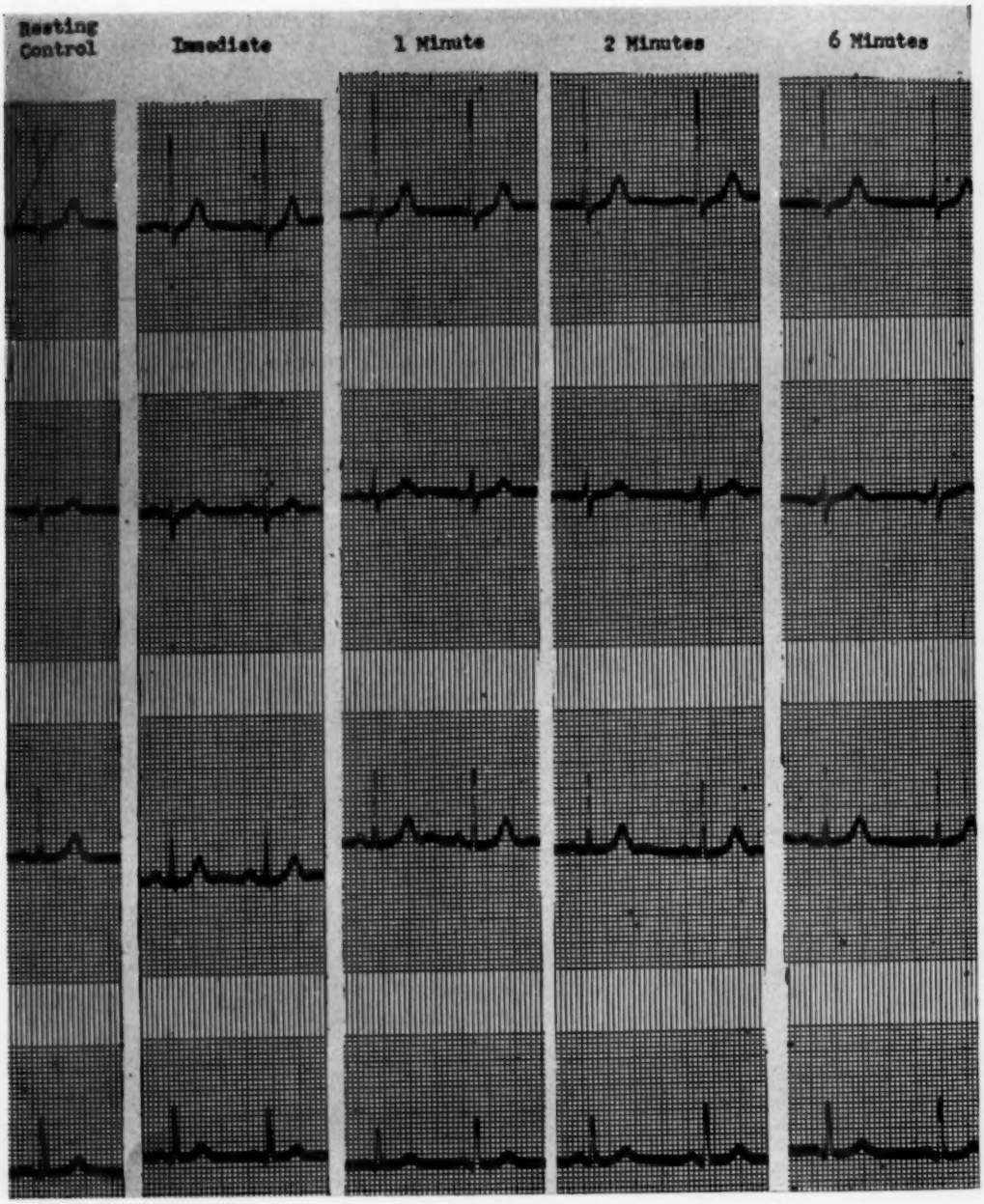


Fig. 2.—The double exercise test of a 33-year-old male (Case 1) with angina pectoris. From above downward are leads V_4, standard Leads III, II, and I.

The ballistocardiogram shows displacement IJ of 0.0012 inch with little evidence otherwise of abnormality. The velocity curve showed the "early M" pattern previously described in the literature.[4] The acceleration curve shows low-amplitude K peak with notching on the acceleration JK segment. The notching on the acceleration JK segment is above the base line in this case, and this unusual shift in phase is probably due to transmission factors in the body and may be related to low natural frequency of the body (three cycles in this case).

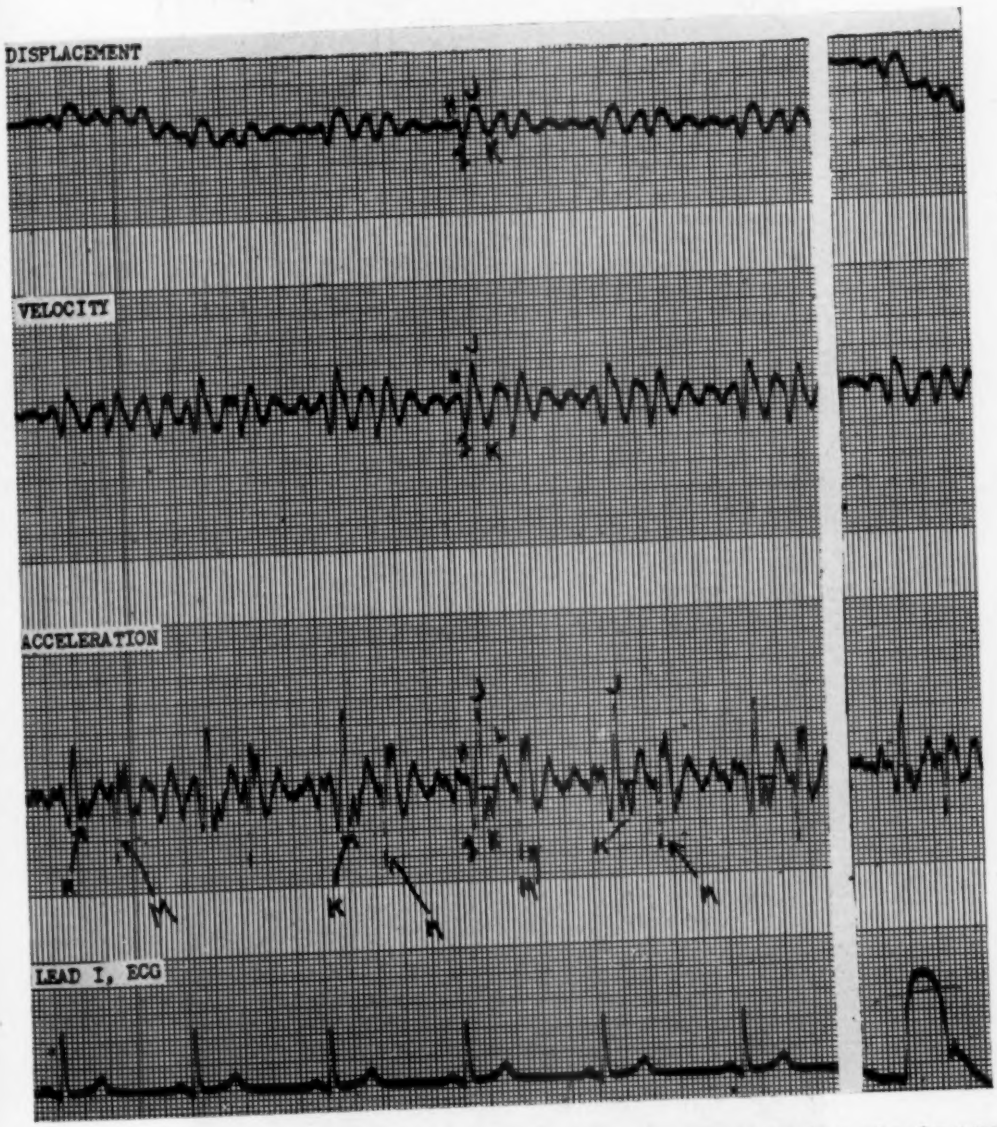


Fig. 3.—Ballistocardiogram on Case 1. Note the marked abnormality present on the acceleration curve which cannot be seen on the displacement curve.

This case developed a myocardial infarction with typical electrocardiogram changes four months after this tracing was taken.

The ballistocardiogram in this case is illustrated in Fig. 4.

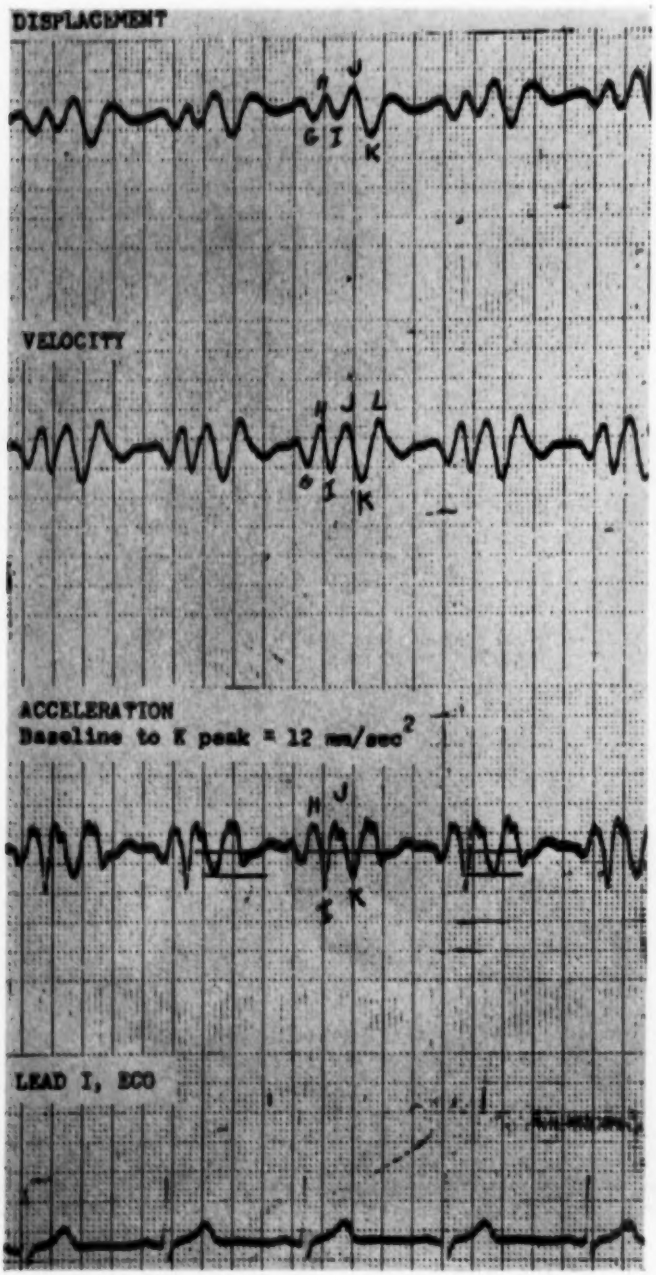


Fig. 4.—A 37-year-old male (Case 2) with angina pectoris.

CASE 3.—A 40-year-old female who complained of severe substernal pain on exertion and on emotional excitement with left-arm radiation was relieved by nitroglycerin. The history was classical for angina pectoris due to coronary heart disease. Blood pressure 120/80 mm. Hg. No murmurs. The resting electrocardiogram was normal. A double "two-step" exercise test was positive with 2 mm. RS-T segment depression and inverted T waves over left chest.

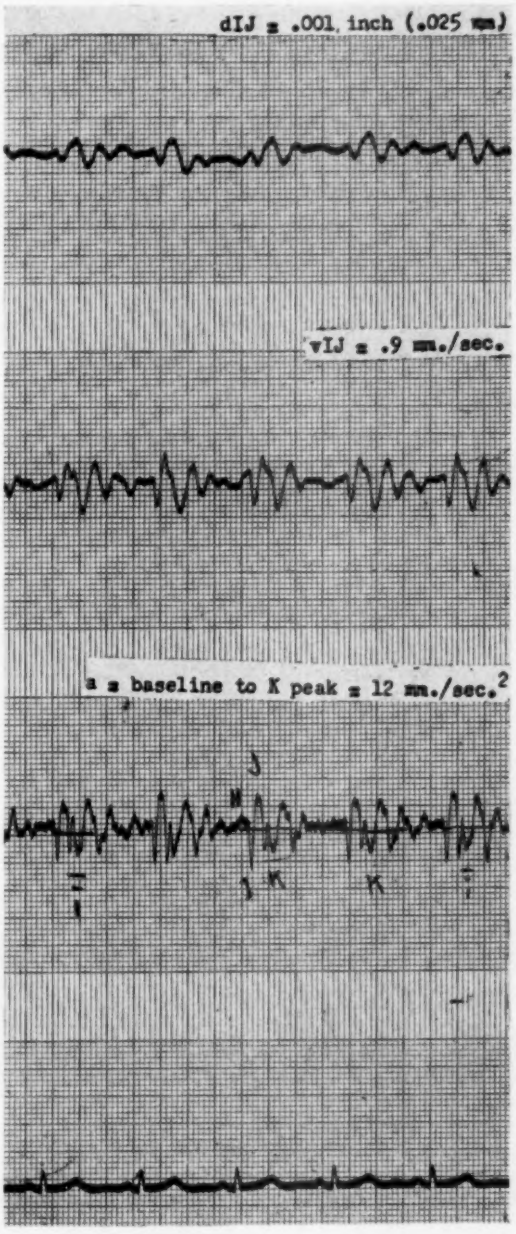
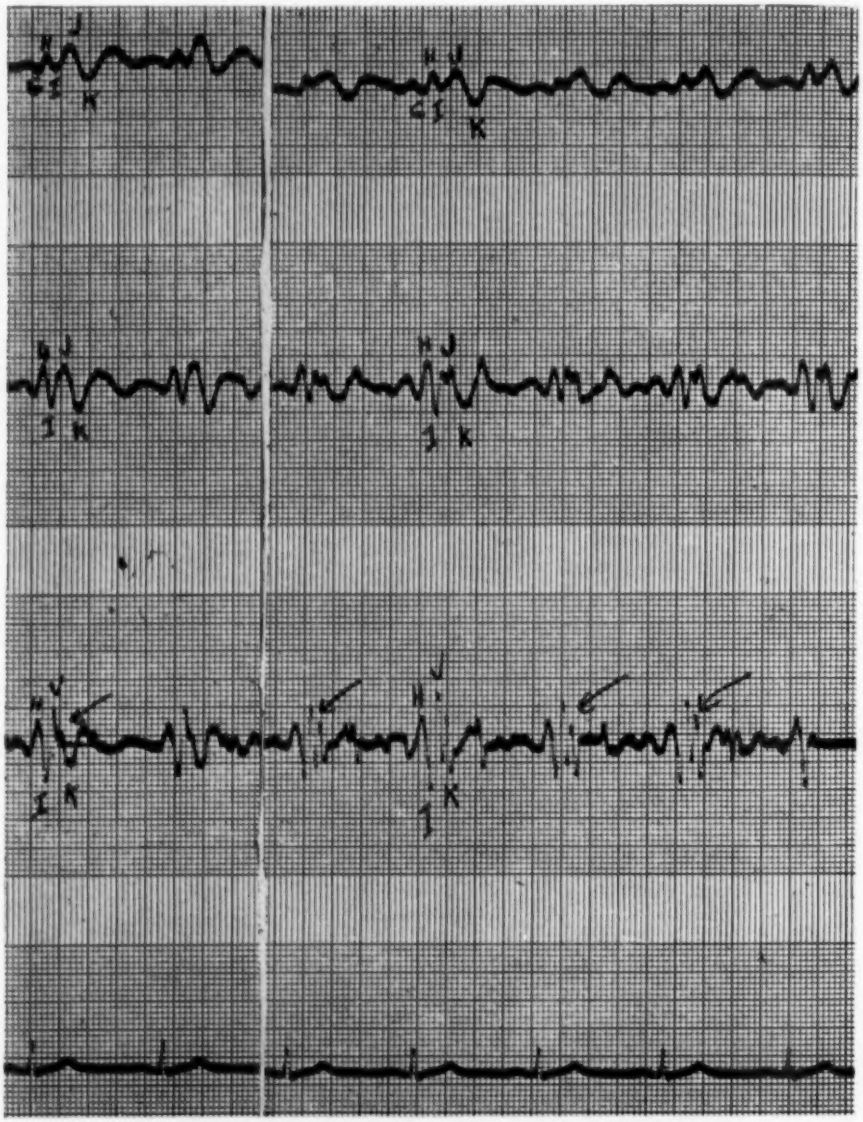


Fig. 5.—Ballistocardiogram of a 40-year-old female (Case 3) with angina pectoris. Form abnormality is much more prominent on the acceleration curve with notching of K peak.

The ballistocardiogram shows displacement IJ of 0.001 inch with essentially normal form. The velocity curve shows low amplitude and slight notching of the JK segment with prolonged timing of 0.12 sec. The acceleration curve shows typical notched K peak and low amplitude, 12 mm./sec.^{2} This case is illustrated in Fig. 5.



A. *B.*

Fig. 6.—Ballistocardiogram of a 46-year-old male (Case 4) with angina pectoris. *A*. Platform frequency, 30 cycles. Note the form changes and the increased amplitudes of the acceleration K peak notching when the platform frequency was lowered (*B*) to 20 cycles (by adding 2 pounds of weight to the platform).

CASE 4.—A 46-year-old male complained of substernal pain on exertion with radiation into both hands. This syndrome had been present over a year before this tracing was taken. He had mild diabetes, well controlled by diet. Blood pressure 120/80 mm. Hg. Physical examination was negative.

The resting electrocardiogram was normal. The single "two-step" test was normal. The

double "two-step" test was equivocal, with RS-T segment depression in Leads I and II over 0.5 mm. but less than 1 mm. with no T-wave changes.

The ballistocardiogram shows displacement IJ of 0.0008 inch with minor abnormality of form with a slowly developing IJ slope. The velocity curve shows a notched J wave and "early M" pattern with low amplitude. The acceleration curves show prominent K peak notching, 15 mm./sec.^{2} from the base line. This case is illustrated in Fig. 6. Note on the illustration that the higher frequency abnormality such as notching of the acceleration K peak can be emphasized by lowering the frequency of the leg piece from 30 to 20 cycles (by adding weight to the platform).

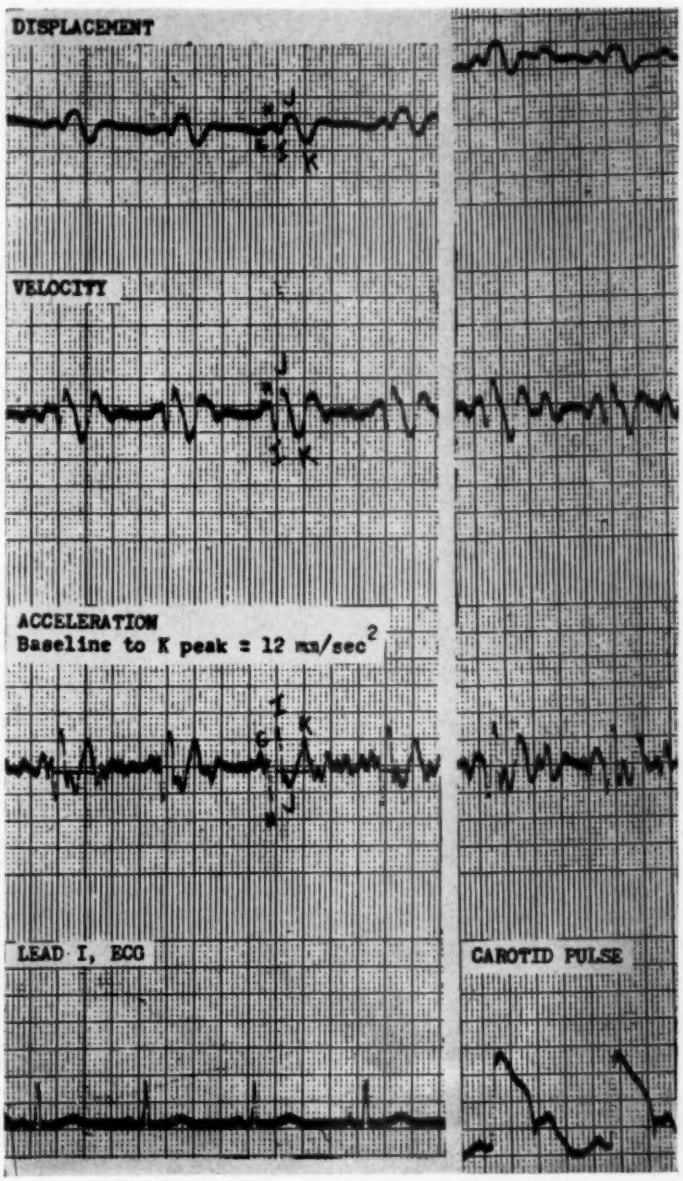


Fig. 7.—Ballistocardiogram of a 45-year-old female (Case 5) with angina pectoris. Displacement IJ amplitude is 0.0008 inch with rounded J peaks. The acceleration curve shows a low-amplitude K peak with notching and 12 mm./sec.^{2} from the base line.

This technique has been described previously[3] and may be useful as a qualitative procedure, since the total system response approaches a linear-type curve above the natural frequency of the body

and tends to compensate for the attenuation of higher frequency components in transmission through the body frame.

CASE 5.—A 45-year-old female complained of severe, cramplike, substernal pains related to exertion which had been present for five years. Pain was considered typical of angina pectoris at onset and of short duration, but was usually followed by hours or days of feeling poorly, with fatigue, and obscured by a strong psychogenic element. Blood pressure, 126/76 mm. Hg.

Many serial electrocardiograms were negative and a single "two-step" was equivocal, RS-T segment depression of 0.8 mm. in Lead II and similar in V_4. No T-wave changes.

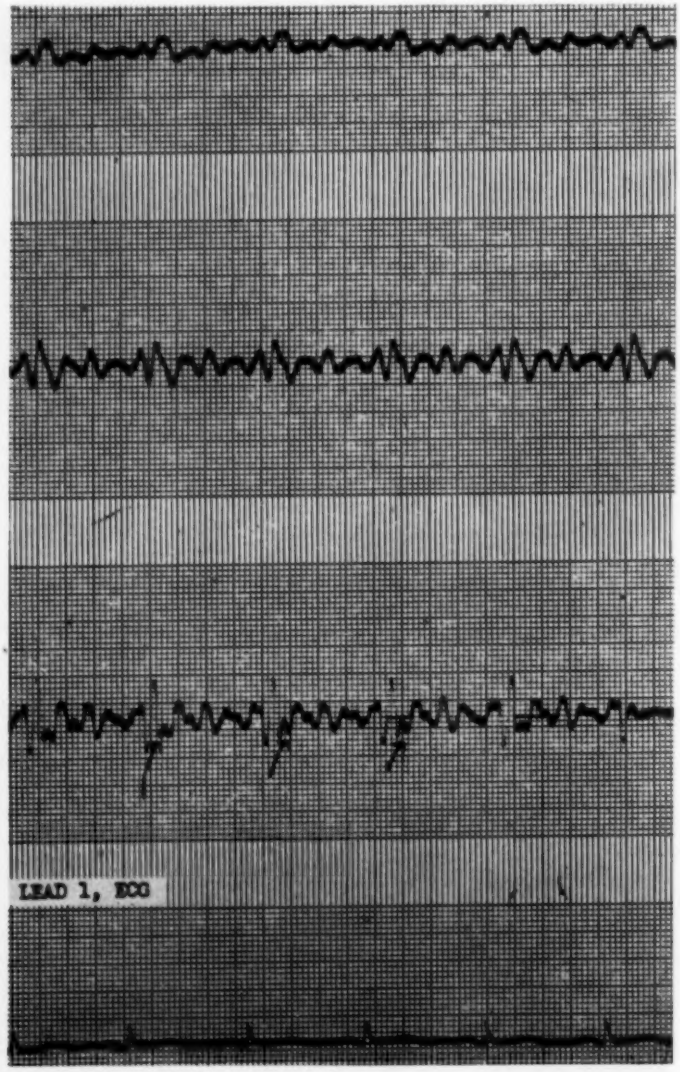


Fig. 8.—Ballistocardiogram of a 43-year-old female (Case 6). IJ displacement = 0.0008 inch. Note rounded peaks of J wave and notched acceleration K waves with 9 mm./sec.^{2} amplitude from base line.

The ballistocardiogram shows low-amplitude displacement IJ of 0.0008 inch and rounding of J peaks. The velocity curves show low amplitude and slight notching of JK segment and prolonged timing, vJK = 0.12 second. The acceleration curves show typical notching of K peak and 12 mm./sec.^{2} in amplitude. Note the labeling of the acceleration curve to conform with nomenclature to be adopted by the American Heart Association. This case is illustrated in Fig 7.

CASE 6.—A 43-year-old female who complained of substernal pressure-type pain usually related to exertion, but sometimes at rest. She had experienced several of these attacks which later were relieved by nitroglycerin but not promptly. She also complained of giddiness not usually related to this pain. Blood pressure 130/80 mm. Hg. Several resting electrocardiograms were normal, but a gradual lowering of T waves was present on Lead I and over left chest on serial tracings. At no time did these T-wave patterns become flat or inverted.

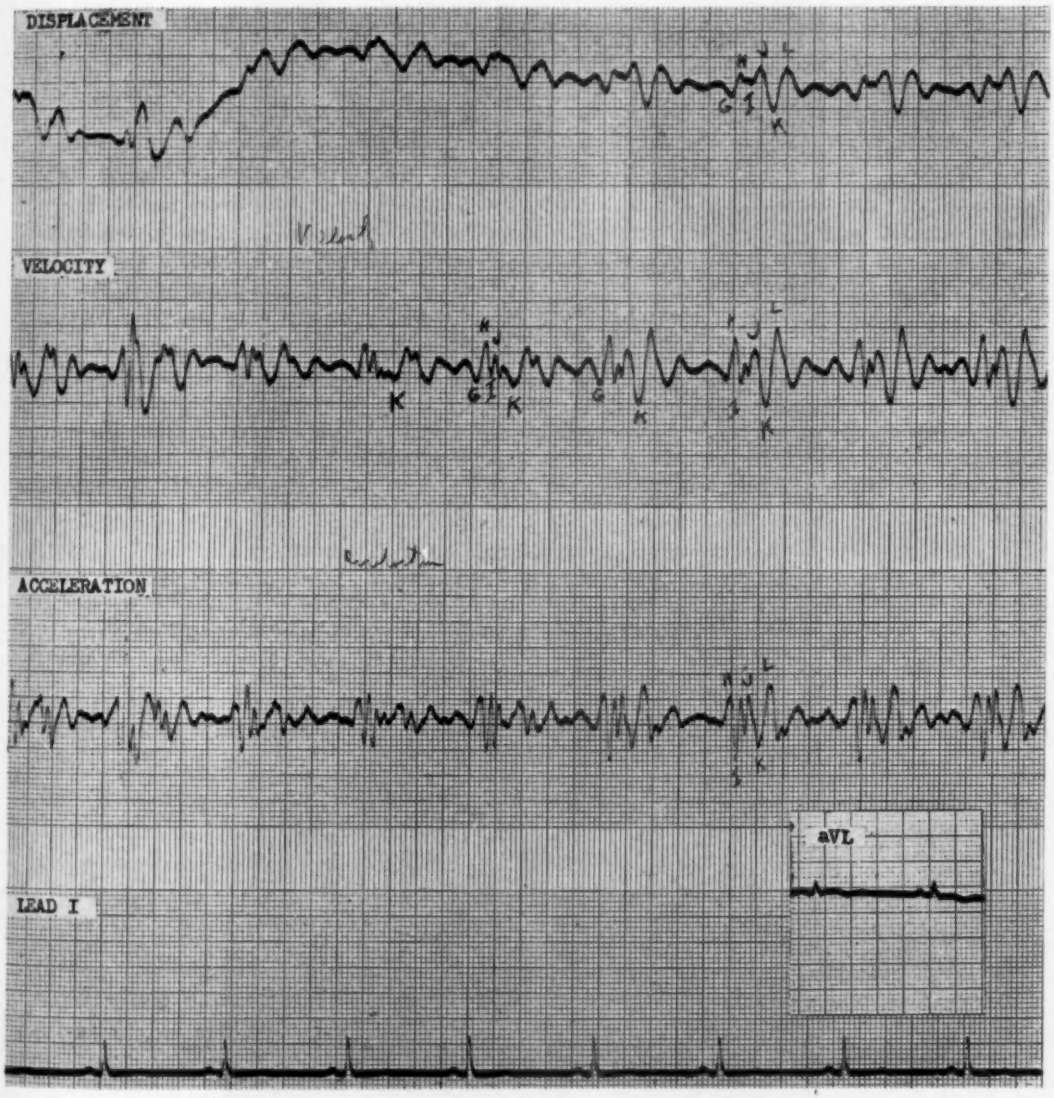


Fig. 9.—Ballistocardiogram of a 48-year-old male (Case 7). The low amplitude and notched I wave on the displacement curve show as a high amplitude and notched acceleration JK segment.

A single "two-step" exercise test showed a positive test with RS-T segment depression of 1.5 mm. over V_4 and deep inversion of T waves in two minutes.

The ballistocardiogram shows displacement IJ of 0.0008 inch with rounded J peaks. The velocity curves show low amplitudes with slight notching of JK segment and prolonged timing, 0.12 second. The acceleration curves show typical K peak notching and 9 mm./sec.^{2} amplitude. This case is illustrated in Fig. 8.

CASE 7.—A 48-year-old male complained of severe substernal pain on exertion which radiated into both arms. He was relieved by nitroglycerin and rest. Blood pressure, 116/70 mm. Hg. Physical examination was negative. The resting electrocardiogram showed low T waves in Lead I, V_4, V_5, and V_6. Inverted T waves in aV_L. This patient refused to try an exercise test

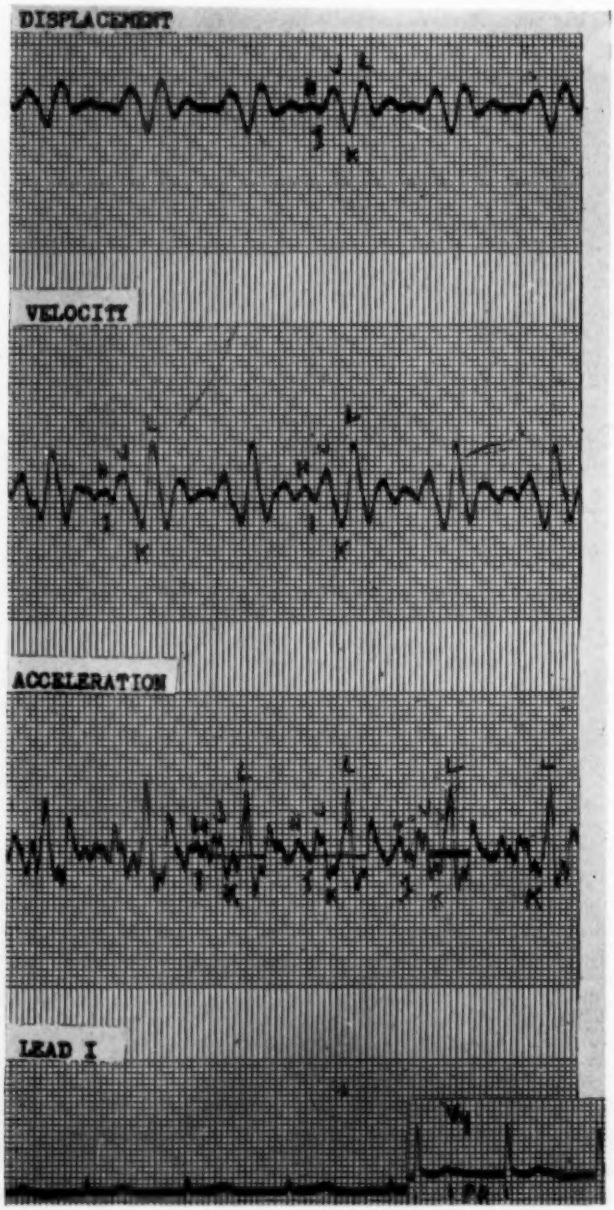


Fig. 10.—Ballistocardiogram of a 53-year-old male (Case 8). The greatest amplitudes are in early diastole with notching of acceleration J and K peaks.

due to fear of pain. He was being considered for administrative action due to the opinion of his supervisors that he was malingering and refused to do lifting and heavy work required in his job. This was accentuated by a physician's report that his electrocardiogram was normal previous to this study and consequent opinion of no heart disease.

The displacement IJ was 0.0008 inch with slight notching of I wave and deep K wave. The velocity curve shows evidence of an "early M" pattern. The acceleration curve shows high-amplitude notch on the acceleration JK segment with K peak of 12 mm./sec.^{2} This case is illustrated in Fig. 9.

CASE 8.—A 53-year-old male sedentary worker was first seen in January, 1952. He had been relatively well until four weeks previous to this examination, at which time he had an episode of dizziness and faintness which occurred at lunch and was associated with morbid pallor and perspiration and fluttering type of chest sensation but no chest pain. Blood pressure, 140/90 mm. Hg. Heart was normal in size with general decrease in sounds. P_2 was increased in intensity, and M_2 was widely split.

No murmurs were heard at rest, but after exercise a mid-diastolic sound was audible but no rumble could be detected. Laboratory work-up showed normal findings, except that a cholecystogram showed small calcified stones with good dye concentration.

Fourteen months later, the patient noted a substernal pressure-type pain in the chest and numbness of the left wrist which occurred usually on exertion, but not always. This pain has become more frequent and severe, sometimes lasting 10 to 15 minutes.

The electrocardiogram showed first degree atrioventricular block with P-R interval of 0.36 second; otherwise normal. The double "two-step" exercise test was normal. The ballistocardiogram shows displacement IJ of 0.0008 inch and deep K wave with high-amplitude L wave. The velocity curve shows small HI and IJ segments with deep K and extremely high L waves. The acceleration curves show notching of J and K peaks, and base line to K peak was 9 mm./sec.^{2} and unusually high L waves. It is probable that the small H waves in this case are associated with the prolonged P-R interval and lend emphasis to previous studies that the H wave is due in part at least, to auricular contraction and flow.[5] This case is illustrated in Fig. 10.

DISCUSSION

It would be presumptuous, at this stage of the development of ballistocardiographic techniques, to believe that the transmission of centrally generated forces would be projected through the body frame without distortions of amplitude and phase. A complex vibration system, such as the body, would need much analysis and study before the techniques used in this paper could be anything but rough empirical measurements which need a conservative approach from the clinical point of view. The results of this study would indicate that the distortions of both amplitude and phase due to body transmission are such that valid clinical data may be obtained.

From the group of cases studied, the diagnostic value of the ballistocardiograph would seem to be much superior to the electrocardiograph in angina pectoris. However, the techniques of measuring motion must again be re-emphasized, since many of these cases could easily show normal ballistocardiograms if unsuitable instrumentation or techniques were used.

The concept of motion measurement should involve certain principles which apply to high-frequency measuring devices such as the Dock technique or high-frequency ballistocardiograph tables before comparative data can be clinically valuable.

1. Instrumentation should have a linear frequency response from $\frac{1}{3}$ of a cycle to at least 16 cycles.

2. Calibration of signal output should be attempted since amplitudes will not be amenable to comparison among clinicians unless this is done.

3. The motion to be measured should approach a single degree of freedom concept, and the distortion produced by the instruments kept at a minimum. Thus, the coupling of the leg piece in the Dock technique should have a natural frequency of about 30 cycles.

4. There should be no ambient vibration interference from the buildings or ballistocardiograph tables to which the instruments are coupled.

It can be shown that when adequate techniques and instrumentation are utilized, a fairly consistent diagnostic pattern can be obtained in angina pectoris due to coronary artery disease. This is true, probably, because coronary heart disease is a simple and uncomplicated hemodynamic event; i.e., the inability of a pump to accelerate blood properly and with adequate ejection forces.

With these techniques, phase and amplitude distortions from the underlying internally impressed forces are limited to transmission through the body and thus enable the clinician to obtain more definitive patterns. When distortions of amplitude and phase occur because of instrumental factors, diagnostic patterns are too hopelessly complex for clinical interpretation since the body transmission factors are also distorting phase and amplitudes to some extent.

It would seem that amplitude distortion is not great due to transmission of these forces through the body frame. Phase distortion is probably greater, as can be seen in the notch pattern of acceleration K wave which may occur, as in Case 2, closer to the J peak. This pattern seems to be related to patients with low body frequency (about 3 cycles), and more knowledge of the body spring constant in relation to the forcing frequency needs to be accumulated. It may well be that resonance between forcing frequency and natural frequency of the body becomes more important in this group, and these cases should be isolated and studied in relation to total system impedance. This will involve much detailed clinical and analytical study. Fortunately for the clinician, individuals with low body frequency have been uncommon in our experience, and form abnormalities can still be shown on the ballistic curves.

CONCLUSIONS

1. The calibrated displacement, velocity, and acceleration ballistocardiograph showed consistent evidence of abnormality in twenty cases of angina pectoris.

2. The ballistocardiogram in this study was a more sensitive index of abnormality than the electrocardiogram.

3. Definitive patterns of abnormality can be obtained in most cases of angina pectoris due to coronary heart disease if instrumentation and techniques are utilized which fit the demands of proper motion measurement.

4. The diagnostic value of signal differentiation (acceleration) has been shown in emphasizing abnormality of form.

CONCLUSIONES IN INTERLINGUA

Pro avantiar le recerca pro methodos objective de evalutar casos atypic de angina de pectore, un serie de 20 patientes de angina de pectore esseva studiate per medio del electrocardiographo (in reposo e in exercitio) e per medio del calibrate ballistocardiographo a barra magnetic que mesura le motion corporee simultaneemente in su componentes de displaciamento, velocitate, e acceleration.

In omne casos le ballistocardiographo revelava signos de anormalitates. In le integre studio le ballistocardiogramma indicava le anormalitates plus sensibilemente que le electrocardiogramma.

Configurationes clarmente indicative de anormalitates es obtenibile per medio del ballistocardiographo in le majoritate del casos de angina de pectore resultante de morbo cardiac coronari si le apparaturas e le technicas usate es adaptate al requirimento de adequate mesurationes de motion.

Grateful acknowledgment is made to Colonel James A. Orbison, U. S. Army Hospital, Fort Belvoir, Virginia, and to Dr. Ruth Benedict and Dr. John M. Evans of the George Washington University Hospital Staff, for their generosity in allowing us to study their cases.

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THE EFFECT OF BLOOD PRESSURE REDUCTION WITH ARFONAD* ON RENAL HEMODYNAMICS AND THE EXCRETION OF WATER AND ELECTROLYTES IN PATIENTS WITH HYPERTENSION

JOHN H. MOYER, M.D., ROBERT MCCONN, M.D., AND RICHARD A. SEIBERT, PH.D.

HOUSTON, TEXAS

WITH THE TECHNICAL ASSISTANCE OF C. POLK SMITH AND ALICE MILNOR, M.A.

THE use of continuous infusions of ganglionic blocking agents has increased the applicability of controlled hypotension for use in some surgical procedures where profuse bleeding from small blood vessels may become a problem. The method is particularly applicable to patients with hypertension since patients with this abnormality are prone to bleed during surgery. If this procedure is to be used generally, it is necessary that observations be made on the effect of blood pressure reduction on vital vascular beds such as the kidney. The current investigation is concerned with measurements of the renal hemodynamic response to blood pressure reduction with Arfonad* in patients with hypertension. This drug is a potent and short-acting ganglionic blocking agent[1] which is used for controlled hypotension during surgery. In addition to renal hemodynamic studies, data were collected on glomerular filtration rate and on the excretion of water and electrolytes. Similar observations which were made on normotensive subjects have been reported previously.[2]

METHODS

Renal function studies were carried out on eight unanesthetized patients with fixed hypertension. Inulin was used to determine glomerular filtration rate (GFR) and para-aminohippurate (PAH) was used to estimate renal plasma flow (RPF). The mean blood pressure was determined by direct intra-arterial manometry, and arterial blood samples for analyses were collected through a manifold. Analytical methods and techniques have been described previously.[3,4]

From the Departments of Pharmacology and Medicine, Baylor University College of Medicine, Houston, Texas.

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*Arfonad is *d*3, 4–(1, 3′–dibenzyl–2′ ketoimidazalido)–1, 2–trimethylene thiophanium *d*-camphor sulfonate which was furnished by Hoffmann-LaRoche, Inc., Nutley, N. J.

All observations were made with the patient in the supine position. Sodium and potassium excretion rates were determined using a Beckman flame photometer for analysis.

After three successive 10-minute control periods, the Arfonad was administered by continuous infusion using a concentration of 1 to 2 mg./c.c. in 5 per cent glucose in distilled water. The infusion rate varied between one and 10 mg./min. with an average of 4 mg. The initial infusion rate was slow, but as the study continued the infusion rate was usually increased in order to obtain maximum reduction in blood pressure. When the initial rate of infusion was very rapid, a precipitous drop in blood pressure frequently occurred. If the blood pressure was reduced gradually over a 10- to 20-minute period, the untoward side effects were both less frequent and much less severe. The infusion was continued and the blood pressure remained depressed for a two to three hour period. Observations were made on renal hemodynamics and on water and electrolyte excretion during the first hour of blood pressure reduction (consecutive 10-minute periods,—D_1 to D_3), and again after two hours (two 10-minute periods,—D_4).

RESULTS

A significant reduction in blood pressure ($p < 0.01$) was obtained in all of the patients to whom Arfonad was administered (Table I). The maximum response for the group was obtained after two hours of drug administration at which time the drug was given at a maximum rate (average of 7 mg./min. for the group). The reduction in systolic pressure was about equal to the reduction in the diastolic pressure. The reduction in blood pressure was frequently associated with a sharp initial depression in renal blood flow which usually returned to or exceeded the control value after two hours of blood pressure reduction. The renal vascular resistance decreased slightly, although this was not statistically significant for the group, except after two hours of blood pressure reduction (period D_4). If the blood pressure had been reduced more rapidly there would have been a greater initial reduction in renal blood flow as has been observed previously following the administration of hexamethonium.[4,5] A slight increase in the pulse rate was frequently observed.

There was an initial depression in glomerular filtration rate in all but one patient. After two hours of blood pressure reduction the glomerular filtration rate remained depressed to about the same degree that was observed initially. In some instances it was depressed more.

The reduction in glomerular filtration rate was associated with concurrent reductions in water excretion ($p < 0.01$) and sodium excretion ($p < 0.01$). These excretion rates remained depressed throughout the entire hypotensive period and did not show any tendency to return toward the control levels. In fact, they actually decreased more as the blood pressure and glomerular filtration rate were reduced further. Potassium excretion was not depressed significantly. The plasma concentration of sodium was not altered significantly. The plasma concentration of potassium was slightly reduced after two hours (Table III).

TABLE I. RENAL HEMODYNAMIC RESPONSE TO BLOOD PRESSURE REDUCTION WITH ARFONAD

PATIENT	MEAN BLOOD PRESSURE MM. HG					RENAL PLASMA FLOW ML./MIN.					RENAL BLOOD FLOW ML./MIN.†					RENAL VASCULAR RESISTANCE‡				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. G.C.	128	117	108	105	106	441	364	368	508	443	711	587	603	833	726	.18	.20	.18	.13	.15
2. G.M.	151	139	132	114	90	717	687	658	671	1161	1156	1108	1061	1048	1814	.13	.13	.12	.11	.05
3. K.O.	154	133	126	109	91	293	213	214	252	278	533	387	382	450	471	.29	.34	.33	.24	.19
4. B.M.	147	119	117	102	100	211	130	134	118	126	306	188	200	176	188	.48	.63	.59	.58	.53
5. S.P.	124	88	84	75	65	284	229	287	185	331	526	424	495	319	561	.24	.21	.17	.24	.12
6. S.L.*	136	123	113	98	90	573	478	544	822	1107	988	797	907	1370	1785	.14	.15	.12	.07	.05
7. W.A.	149	136	126	105	87	428	460	377	361	478	751	807	589	602	771	.20	.17	.21	.17	.11
8. W.M.	155	134	133	112	96	373	340	345	318	396	549	500	493	482	550	.28	.27	.27	.23	.17
Mean (8 patients)	143	124	117	103	91	415	363	366	404	540	690	600	591	660	858	.24	.26	.25	.22	.17
P Value <**		.01	.01	.01	.01		.02	.01	NS	.20		.02	.01	NS	.30		NS	NS	NS	.02
Per cent of control		87	82	72	64		87	88	97	130		87	86	96	124		108	104	92	71
Normotensive subjects§																				
Mean Value	98	81	75	65	57	660	455	489	419	301	1143	774	822	697	504	.09	.10	.12	.10	.15
P Value <**		.02	.01	.01	.01		.05	.02	.01	.01		.02	.02	.01	.01		NS	NS	NS	.30
Per cent of control		83	77	66	58		69	74	63	46		68	72	61	44		111	133	111	167

† — Renal blood flow = $\frac{\text{Renal plasma flow}}{1 - \text{Hematocrit}}$

‡ — Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

NS = Not statistically significant $P > 0.30$

§ — Nine subjects were studied

* — During infusion of norepinephrine, mean blood pressure = 130; renal plasma flow = 955

** — $t = \bar{x}\sqrt{\frac{N(N-1)}{S\,x^2}}$

C = Control, average of three 10-minute periods

D_1 = Average of first two 10-minute periods after infusion of Arfonad started

D_2 = Average of third and fourth 10-minute periods after infusion of Arfonad started

D_3 = Observations (average of two 10-minute periods) made one hour after infusion of Arfonad started

D_4 = Observations made (average of two 10-minute periods) made two hours after infusion of Arfonad started

TABLE II. EFFECT OF BLOOD PRESSURE REDUCTION ON GLOMERULAR FILTRATION RATE AND WATER AND ELECTROLYTE EXCRETION

PATIENT	GLOMERULAR FILTRATION RATE ML./MIN.					URINE VOLUME ML./MIN.					SODIUM EXCRETION μEQ./MIN.					POTASSIUM EXCRETION μEQ./MIN.				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1. G.C.	72	66	68	72	84	5.4	3.1	1.0	1.0	1.2	231	264	157	153	218	20	18	26	22	29
2. G.M.	113	101	111	97	78	4.6	2.2	0.8	0.7	0.6	329	191	107	79	58	73	63	69	87	135
3. K.O.	78	61	62	63	73	8.2	2.5	1.2	1.3	0.8	508	178	191	169	99	67	38	41	51	54
4. B.M.	41	26	28	21	24	7.0	5.2	2.3	1.1	2.4	614	262	147	80	97	47	29	28	26	31
5. S.P.	81	48	49	26	36	1.7	1.4	0.6	0.2	0.6	278	122	82	38	51	33	31	40	23	44
6. S.L.*	93	77	88	86	77	8.1	2.3	1.1	0.9	1.1	307	232	161	128	79	45	35	36	51	75
7. W.A.	141	138	106	96	114	13.2	12.8	3.6	0.8	0.8	144	133	101	76	96	35	37	31	34	57
8. W.M.	81	58	56	46	43	13.5	6.4	2.9	1.8	1.1	407	210	151	112	70	46	50	52	47	68
Mean	88	72	71	63	66	7.7	4.5	1.7	1.0	1.1	352	199	137	104	96	46	38	40	43	62
P Value <		.01	.01	.01	.02		.02	.01	.01	.01		.02	.01	.01	.01		.10	.30	NS	.20
Per cent of control		82	81	72	75		58	22	13	14		57	39	30	27		83	87	93	135
Normotensive subjects§																				
Mean value	121	96	94	86	64	3.9	3.2	1.5	1.0	0.7	161	115	91	66	48	56	49	49	49	53
P Value <		.02	.01	.01	.01		NS	.02	.01	.01		.10	.01	.01	.01		.05	.20	NS	NS
Per cent of control		79	78	71	53		82	38	26	18		71	57	41	30		88	88	88	95

C — D_4 — See Table I for key to abbreviations
* — During infusion of norepinephrine, urine volume = 5.4 ml./min.; sodium excretion = 485 μEq./min.; potassium excretion = 84 μEq./min.; and glomerular filtration rate = 115 c.c./min.
§ = Nine subjects studied
NS = Not statistically significant

TABLE III. SIDE REACTIONS AND EFFECT ON HEMATOCRIT AND PLASMA ELECTROLYTES

PATIENT	HEMATOCRIT			PLASMA CONCENTRATION						SIDE EFFECTS	RACE* SEX*	AGE
				SODIUM mEq./L.			POTASSIUM mEq./L.					
	C	D_2	D_4	C	D_2	D_4	C	D_2	D_4			
1. G.C.	38	39	39	137	135	135	4.2	4.1	4.1	None	WF	27
2. G.M.	38	38	36	139	139	137	4.1	4.0	3.3	Restless, cold, weak	WF	36
3. K.O.	45	44	41	127	128	131	4.9	4.8	4.4	None	NM	58
4. B.M.	31	33	33	136	135	133	4.4	4.3	4.1	None	NF	40
5. S.P.	46	42	41	133	133	130	5.2	5.2	4.6	Extremely sensitive to drug	WF	32
6. S.L.	42	40	38	127	127	123	4.0	4.0	3.3	Fatigue, headache, nausea	NF	34
7. W.A.	43	36	38	131	131	130	4.6	4.1	3.9	None	NF	38
8. W.M.	32	30	28	128	128	127	3.8	3.8	3.3	Nausea	NF	54
Mean	39	38	37	132	132	131	4.4	4.3	3.9			
P Value <		.20	.05		NS	NS		NS	.01			
Per cent of control		97	95		100	99		98	89			
Normotensive subjects§												
Mean Value	41	39	39	142	142	138	4.6	4.4	4.0			
P Value <		.20	.02		NS	NS		.01	.01			
Per cent of control		95	95		100	97		96	87			

C — D_4 — See Table 1 for key to abbreviations
* — W = White; N = Negro; F = Female; M = Male
§ — Nine subjects studied
NS — Not statistically significant, $P > 0.30$

Nausea was associated with blood pressure reduction in two instances. Two of the patients complained of extreme weakness, and a third became progressively more restless as the blood pressure decreased.

DISCUSSION

The tendency for Arfonad to produce a greater depression of glomerular filtration rate in normotensive than in hypertensive individuals is probably due to blood pressure reduction to a lower absolute value in the former (Tables I and II). As a result adequate compensatory renal vasodilation was not possible in these patients. This response should be anticipated since critical levels of blood pressure are being approached beyond which the intravascular pressure is inadequate to maintain filtration through the glomerular membrane.[6,7] When the pressure is reduced below this critical level, glomerular filtration drops off rapidly.[7] The current data would indicate that renal blood flow is depressed at about the same blood pressure range that glomerular filtration is, possibly due to inadequate hydrostatic pressure to force the blood through the renal blood vessels. When the blood pressure was reduced from hypertensive levels to normotensive levels, renal vasodilation was adequate after two hours so that renal blood flow approximated the control values. However, when the blood pressure in normal subjects was reduced to the marked hypotensive levels that are possible with the administration of Arfonad, this compensation was inadequate. As a result, renal blood flow was and remained markedly depressed (Table I).

The reduction in water and electrolyte excretion is probably a reflection of the reduction in glomerular filtration rate without concurrent impairment of tubular reabsorptive mechanisms.[7] As a result, the percentage of filtered water and sodium that was reabsorbed was greater but the absolute amount was probably less. This would seem to be a point worth noting if intravenous fluids are to be administered in a large amount during surgical procedures which require controlled hypotension. There was no significant difference between the response of the normotensive subject and the hypertensive patient.

The degree of blood pressure reduction that can be obtained with Arfonad is considerably greater than that which is obtainable with other ganglionic blocking agents, such as hexamethonium and Pendiomide.* This probably accounts for the sustained depression in renal blood flow that occurs when maximum reduction in blood pressure is obtained with Arfonad as compared to hexamethonium[5] in the normal individual. No doubt the increased hypotensive effectiveness also accounts for the greater reduction in glomerular filtration rate with Arfonad than is seen with hexamethonium and Pendiomide.

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*Pentamethyl-diethyl-3-aza-pentane-1, 5-diammonium-dibromide, Ciba Pharmaceutical Products, Inc., Summit, N. J.

SUMMARY AND CONCLUSIONS

1. Arfonad was administered by continuous intravenous infusion to eight patients with hypertension. Observations were made on renal hemodynamics and on the excretion rates of water and electrolytes over a two-hour period of blood pressure reduction.

2. As the blood pressure was reduced, glomerular filtration rate and water and sodium excretion were depressed and remained so during the entire period of blood pressure reduction.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Le uso de continue infusiones de blocantes ganglionic ha augmentate le potential practic de hypotension dirigite in certe interventiones chirurgic in que un profuse sanguination ab parve vasculos sanguinee pote devenir un problema. Le application general de iste methodo prerequire observationes in re le effecto del reduction del pression sanguinee super varie sitos vascular vital.

Le presente reporto concerne octo patientes hypertensive a qui le hypotensor Arfonad esseva administrate per continue infusion intravenose. Esseva facite in iste patientes observationes del hemodynamica renal e del excretion de aqua e del electrolytos durante un periodo de reducite pression sanguinee de duo horas.

Quando le pression sanguinee esseva reducite le ratas del filtration glomerular e del excretion de aqua e de natrium esseva abassate e remaneva basse durante le integre periodo del reducite pression sanguinee.

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CHARACTERISTICS OF THE HIBERNATING HEART

A. R. Dawe, Ph.D., and P. R. Morrison, Ph.D.

Madison, Wis.

INTRODUCTION

If the body temperature of a mammal is lowered sufficiently, the heart will slow and stop. Under usual conditions, this end point at which the heart of the intact mammal will stop beating is attained at a body temperature of very nearly 16° C. (Martin and Applegarth,[1] Tait[2]—isolated heart; Britton,[3] Lutz[4]—intact heart; Crismon[5]—many references). Lower temperatures, however, for heart standstill have been observed (Langendorff[6]—isolated heart; Crismon[5]—intact heart). In the case of the hibernating heart, body temperatures may drop physiologically to values as low as 0° C. (Chao, Iping, and Yeh)[7,8] with detectable heart contractions continuing, and without constituting a lethal condition. It is therefore probable that the only condition under which the lowest temperature characteristics of the intact mammalian heart can be known physiologically is that of the hibernating heart. The characteristics of the hibernating heart rate, and of the electrocardiographic components which can be observed within the dimensions of the single heart beat, with particular reference to body temperature, constitute the subject of this paper.

METHODS

Hedgehogs, *Erinaceus europaeus*, Arctic ground squirrels, *Citellus parryi*, and Franklin ground squirrels, *Citellus franklini*, were utilized. In the late fall and early winter of 1952, prior to hibernation, animals were prepared for study by the attachment of appropriate thermocouple terminals and electrodes onto the skin. These consisted of a thermocouple terminal deeply inserted into the scruff of the neck, a second thermocouple terminal deeply inserted into the skin of the back just anterior to the base of the tail, and three stainless steel safety pins, one each in the skin on the lateral side of the upper portions of the hind limbs and of the right forelimb. Animals were then placed in hibernacula which featured the conditions necessary for the induction of hibernation. These conditions were darkness, relative confinement, appropriate nesting material, ambient temperatures as that of the outside air, and a minimum of food and water. The thermocouple terminals and electrodes in time healed into place.

From the Departments of Physiology and Zoology, University of Wisconsin, Madison, Wis.
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Many of the animals entered the hibernating state. When it was desired to obtain data from the hibernating animal, it was carefully removed from the hibernaculum by a technique involving a minimum of disturbance to the animal. Stimuli of light, heat, and sound were reduced to the barest minimum when removing the hibernating animal to the laboratory. In this respect our observations are in complete agreement with other investigators, for example Mills,[9] who have also noted the extreme sensitivity of the hibernating animal, and the extreme ease with which it can be aroused from its hibernating state. The animal was then placed in a metabolism chamber specially prepared for its reception. Wires to a Leeds and Northrup 8-point thermocouple recorder were clipped to the thermocouple terminal wires emerging from the animal's skin. Wires to a Sanborn 4-channel electrocardiograph were clipped to the three safety pins in the skin of the limbs, for the purpose of obtaining heart rates and Lead II electrocardiograms. The chamber was sealed, and the wires emerged through sealed stoppers. A continuous oxygen supply was introduced. Oxygen uptake measurements were begun by the Morrison[10] closed-circuit method. The chamber containing the animal was lowered into a tank of cold water. This tank was equipped with a cooling unit controlled by a thermoregulator which permitted temperature settings at values from 0° C. up to room temperature values of about 24° C. Continuous records were begun of oxygen consumption, heart rate, electrocardiograms, and body temperatures fore (T_F) and hind (T_R). If heart rate only was desired, the paper speed on the Sanborn was set for slow, on the other hand if electrocardiograms were desired, the paper speed was set at fast (50 mm./sec.). A thermocouple was immersed in the water bath to obtain continuous ambient (T_A) temperatures. At the times that the animal remained in hibernation in the chamber, data were collected continuously. If the animal aroused from hibernation it often broke its electrical connections so that data could no longer be collected. In such cases it was necessary to remove it from the metabolism chamber and return it to the hibernaculum. In a number of cases the animals spontaneously aroused from hibernation without electrical disconnections. In these cases animals again dropped back into deep hibernation. In this way we were fortunate enough to obtain data on the animal *going into* hibernation. The data is therefore admissible as of three categories: data collected *going into* hibernation, data collected *in* deep hibernation, data collected *coming out* of hibernation, (*arousal*).

The intervals in the small mammal electrocardiograms to be reported upon here were measured in thousandths of inches using a toolmaker's microscope accurate to 0.001 ± 0.0005 inch. In all electrocardiograms measured, a Q wave was lacking. The intervals were measured as follows:

a. The P interval was measured from the beginning of the P wave to its peak, this value doubled to obtain a P-interval value.

b. The P-R interval was measured from the beginning of the P wave to the beginning of the R wave.

c. The QRS was measured from the beginning of the R wave to the inflection point of the S wave.

d. The Q-T interval was measured from the beginning of the R wave to the end of the T wave.

e. The RS-T interval was measured from the inflection of the S wave to the peak of the T wave.

f. The T-P interval was measured from the end of the T wave to the beginning of the P wave.

By considering the fact that there is no Q wave, all of these measurements approach as nearly as possible classical measurements in the human electrocardiogram. The RS-T segment differs somewhat, but it nevertheless largely includes the repolarization segment.

Physiologically, the previously mentioned intervals are taken to represent in time measures of the following physiologic processes:

a. The P interval represents auricular depolarization.
b. The P-R interval represents conduction time through the heart.
c. The QRS represents ventricular depolarization.
d. The RS-T interval represents ventricular repolarization.
e. The T-P interval inversely represents a measure of SA node automaticity.

RESULTS

A. *Heart Rates.*—Heart rates were obtained on the three species in the experimental series. These experiments lasted an hour or two in several instances, but in other instances lasted for periods of several weeks. A typical experiment (327) utilizing the hedgehog is shown in Fig. 1. This experiment lasted for 6 days. The figure shows the changes in body temperature and heart rate as the animal spontaneously aroused and went back into hibernation three times during those 6 days. It is of interest that in all experiments the rise in heart rate in arousal preceded the rise in body temperature, thus substantiating Lyman and Chatfield's[11] observations in this respect. Experiment 327 has been depicted in another way, as shown in Fig. 2, in which the heart rate has been plotted as a function of the hind-skin temperature. It indicates the hysteresis of the heart rate - body temperature function as the animal enters hibernation. It is apparent that the heart rate - body temperature function is totally different in arousal from its function going into hibernation. Of interest also is the sharp break in the curve at body temperatures of about 20° C. as the animal goes into hibernation, indicating a hyperirritability of the heart in spite of a lowering body temperature. It is this break in the curve which is lacking in the nonhibernating animal, and which distinguishes the hibernating heart from the nonhibernating heart at this critical juncture. The same phenomenon was noted in graphical representations of Arctic ground squirrel heart rate - body temperature values.

When the animal reached deep torpor in hibernation, the T_F and T_R values were always within 1° of each other, and the heart rate stabilized at this low body temperature. Graphical representations of heart rates and body temperatures as they stabilized in deep hibernation are shown in Figs. 3 and 4. The ranges of heart rates and body temperatures observed for animals stabilized in deep hibernation are as follows:

Animal	*Body Temperature*	*Heart Rate*
Hedgehog	3.0–12.0° C.	3–15/min.
Franklin ground squirrel	3.8– 4.0° C.	2–4/min.
Arctic ground squirrel	0.5– 9.0° C.	2–7/min.

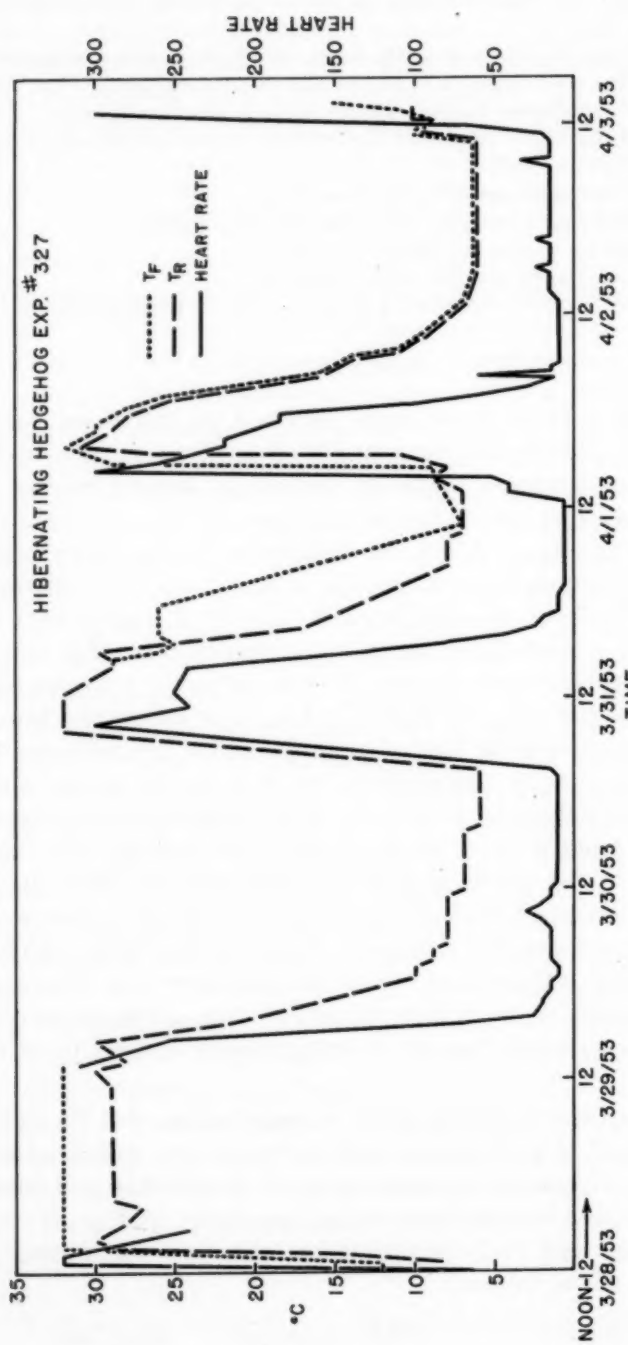

Fig. 1.—Hedgehog. The animal *goes into* hibernation, remains *in* hibernation, and *comes out* of hibernation three and one-half times in six days. T_F indicates temperature as recorded from fore thermocouple. T_R indicates temperature as recorded from hind thermocouple.

The ambient temperature in the cases of animals in deep hibernation ranged from 0.8° C. above the body temperature to as much as 6.8° C. below the body temperature, and in almost every case below the body temperature. Stating it conversely, in almost every case the body temperature (T_B) was held somewhat above the ambient temperature (T_A). The average amount by which

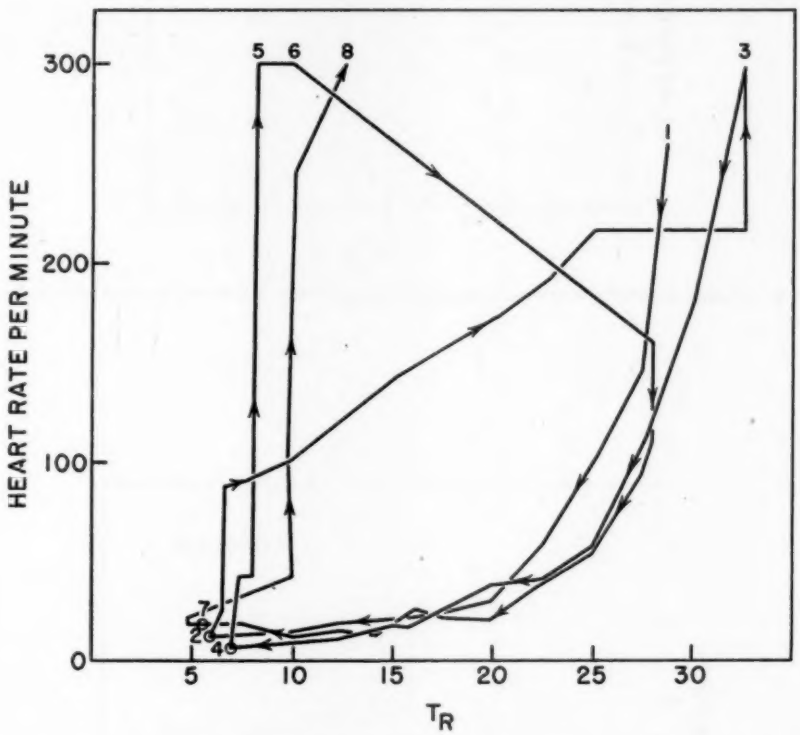

Fig. 2.—Continuous record (Experiment 327) of heart rate and body temperature (T_R = rear skin temperature), showing hedgehog going into, in, and coming out of deep hibernation three times in five days. Times of events as indicated numberically on the graph are as follows:

1.	14:00	3/29/53	5.	17:00	4/1/53
2.	03:00	3/30/53—03:00 3/31/53	6.	18:00	4/2/53
3.	12:00	3/31/53	7.	06:00	4/2/53—10:00 4/3/53
4.	01:00–13:00	4/1/53	8.	12:00	4/3/53

T_B exceeded T_A was 2.1° C. This compares favorably with Johnson's[12] values of 2.0 to 3.0° C. for the 13-lined ground squirrel. Heart rates stabilized in hibernation at very low body temperatures and at ambient temperatures of about 2.0° C. below the body temperature values. Thus, a heart rate of 5 per minute at a T_B value of 6° C. would be obtained at a T_A value of about 4° C.

The lowest heart rate observed was seen in Experiment 302 taken on a Franklin ground squirrel. A rate of 2.2 beats per minute was recorded in this experiment on Jan. 26, 1953, at 09:45 A.M. when $T_A = 3.0°$ C., $T_F = 3.8°$ C., and $T_R = 3.8°$ C.

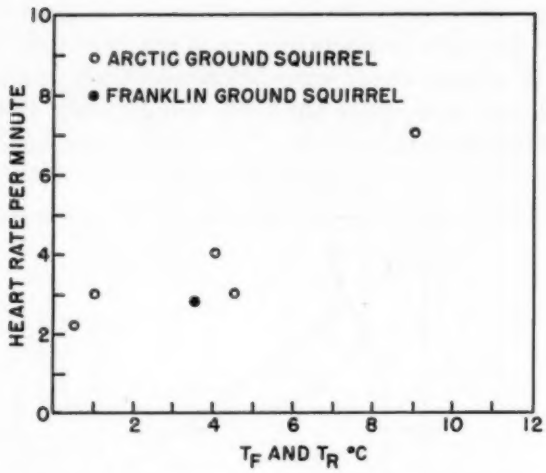

Fig. 3.—Points at which heart rate and body temperature stabilized in deep hibernation.

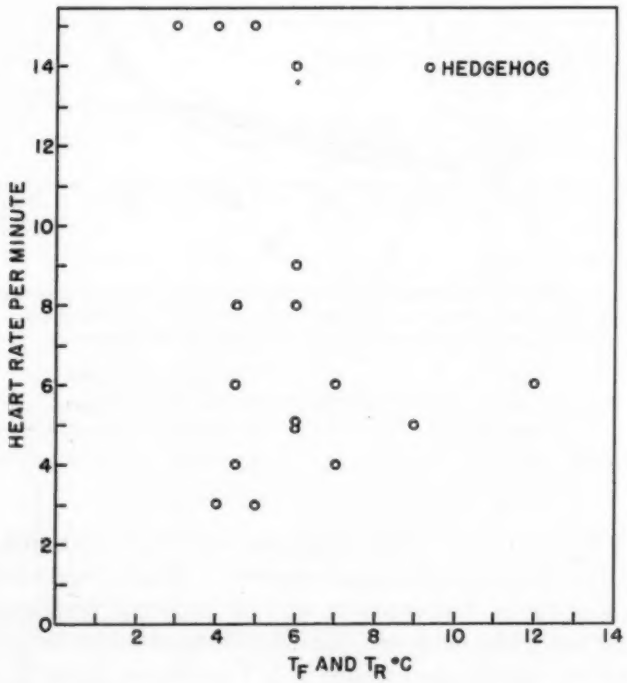

Fig. 4.—Points at which heart rate and body temperature stabilized in deep hibernation.

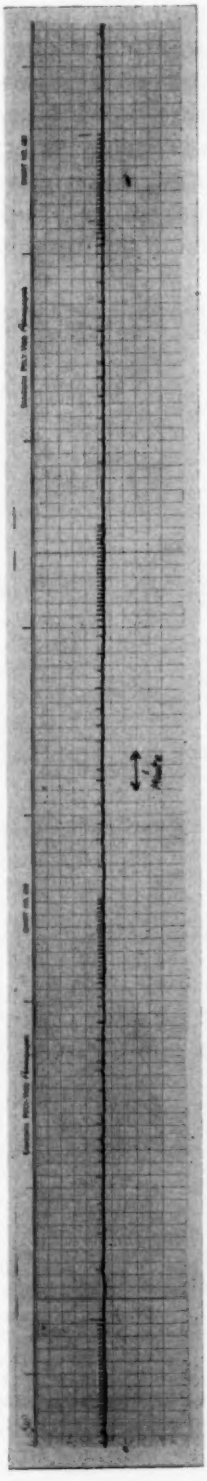

Fig. 5.—Franklin ground squirrel (Experiment 302) at 13:00—1/24/53—animal in deep hibernation. T_F and T_R = 3.2° C. Electrocardiographic tape set at very slow speed. Notice the pattern of bursts of heart beats followed by relatively few beats, then a recurrence of the burst of beats. This heart-beat pattern was observed to continue for a period of 72 hours.

On several occasions unusual heart rate patterns were observed in deep hibernation. In the Arctic ground squirrel on one occasion the heart showed paired beats for a considerable period. This phenomenon was also reported by Endres and associates[13] as occurring in the hibernating marmot heart. In the Franklin ground squirrel and the hedgehog a very unusual rate pattern was noted which can only be described as bursts of heart beats. This pattern continued for many hours, and in the case of one Franklin ground squirrel it continued for several days. An example of this machine-like rhythm is shown in Fig. 5.

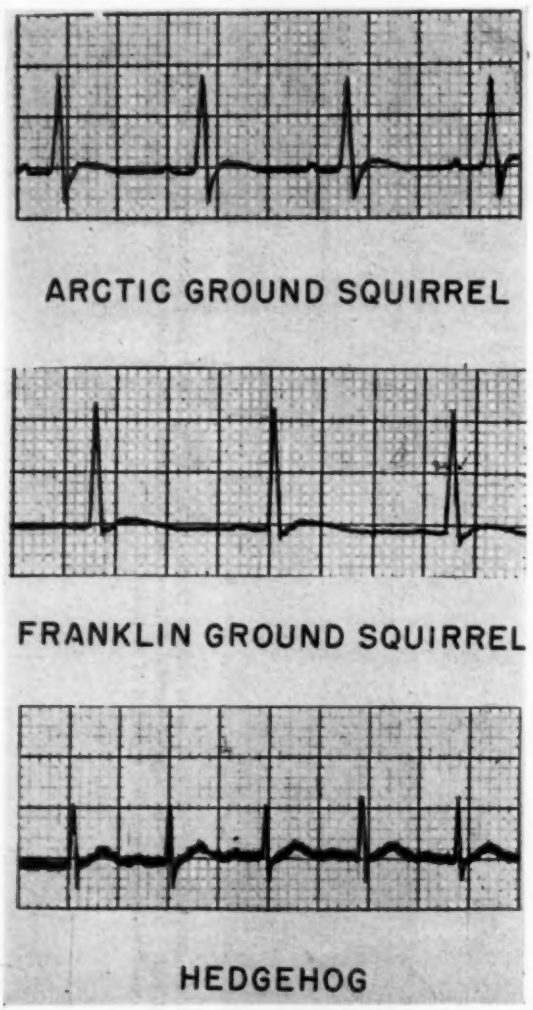

Fig. 6.—Electrocardiograms of Arctic ground squirrel, Franklin ground squirrel, and hedgehog taken at times of light Nembutal anesthesia. Rectal temperatures at times of these ECGs were as follows: Arctic ground squirrel = 32.5° C.; Hedgehog = 32.0° C.; Franklin ground squirrel = 33.7° C. These ECGs should be compared to ECGs taken in hibernation (Figs. 7, 8, 9). Ten heavy lines horizontally = 1 second. Two heavy lines vertically = 1 mv.

B. *Electrocardiograms.*—Typical normal electrocardiograms (ECGs) for the three species are shown (Fig. 6). These ECGs were obtained on lightly

Nembutalized animals in which body temperature was about 5° C. less than normal values as defined by Ryser.[14] They are included for comparative purposes.

Electrocardiograms of hibernating animals were taken periodically while animals were in deep hibernation (Figs. 7, 8, 9). It was apparent that in this slowly beating heart the normal ECG components had been lengthened. This lengthening of ECG components can be thought of as an extension or "stretching", indicating that the reaction times of the cardiac processes involved were increased. The lengths (times) of the components of the electrocardiogram

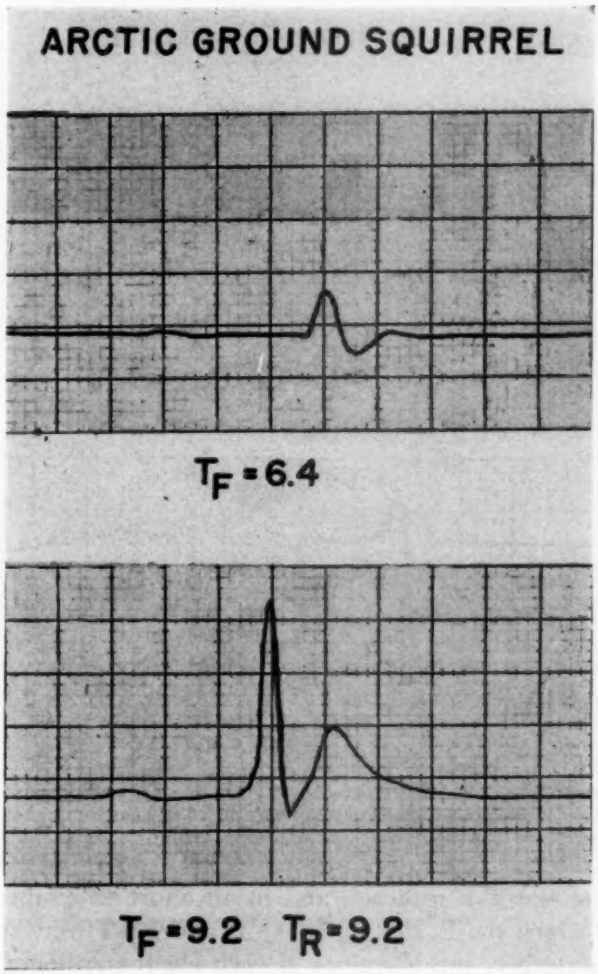

Fig. 7.—Representative electrocardiograms of Arctic ground squirrels in deep hibernation. T_F = front skin temperature. T_R = rear skin temparature. Ten heavy lines horizontally = 1 second. Two heavy lines vertically = 1 mv.

taken from the hibernating animal therefore were compared arithmetically to average components from electrocardiograms taken from nonhibernating individuals of the same species. This was done by dividing the value (in seconds) for the average normal ECG component into the value (in seconds) for the hibernating ECG component. The division of one by the other gave a "factor

of stretch" for each component, hereinafter designated as K. Thus if the P-R interval had an average value of 0.05 sec. in the normals, and if the P-R interval in a given electrocardiogram taken in deep hibernation was 0.60 sec., the amount by which the component was stretched was 0.60/0.05 = 12 times. The value "12" is the factor of stretch, or K.

The average K values have been plotted in Fig. 10 for each ECG component. As can be observed, the T-P interval was grossly stretched, the P-R interval next so, and the other intervals less so.

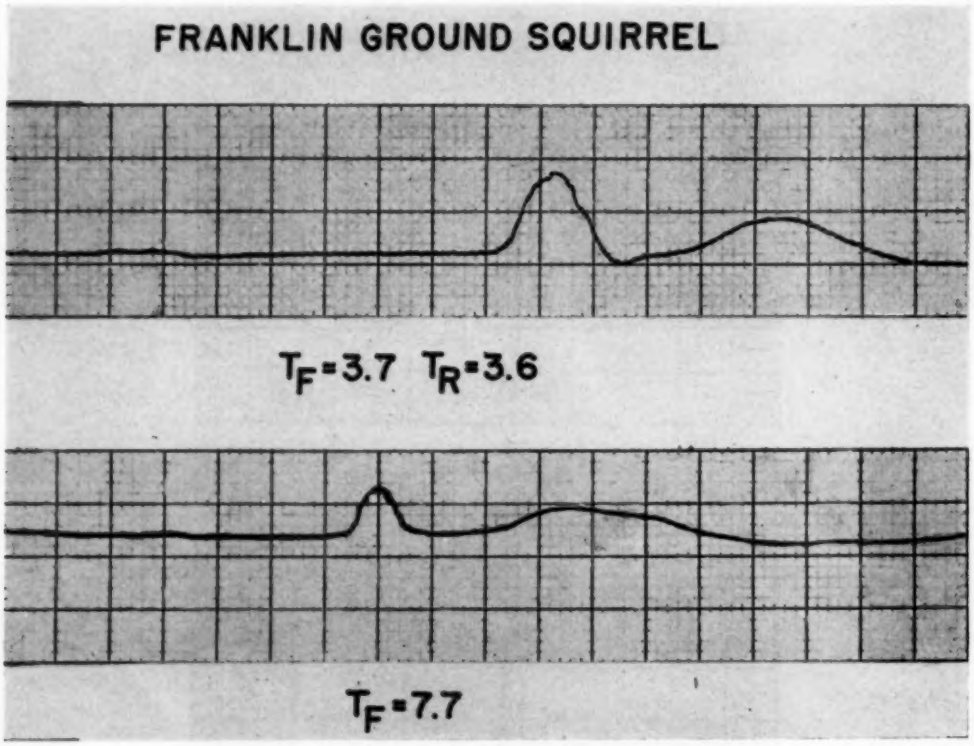

Fig. 8. —Representative electrocardiograms of Franklin ground squirrels in deep hibernation. T_F = front skin temperature. T_R = rear skin temperature. Ten heavy lines horizontally = 1 second. Two heavy lines vertically = 1 mv.

By excepting the T-P interval, and in an effort to evaluate more exactly the amounts by which the P, P-R, QRS, Q-T, and RS-T were stretched by comparison with each other, the K values in each electrocardiogram for each component were arranged in a series from largest to smallest and assigned magnitude of stretch symbols designated as S_1, S_2, S_3, S_4, and S_5 in descending order of magnitude.

Thus if the K values for a given electrocardiogram were as follows:

P = 2.1
P-R = 10.3
QRS = 7.4
Q-T = 3.1
RS-T = 4.0

The S values would be:

S_1 = P-R
S_2 = QRS
S_3 = RS-T
S_4 = Q-T
S_5 = P

In other words, in the particular ECG cited above, the P-R interval is stretched most, the QRS next, then the RS-T, the Q-T, and finally the P.

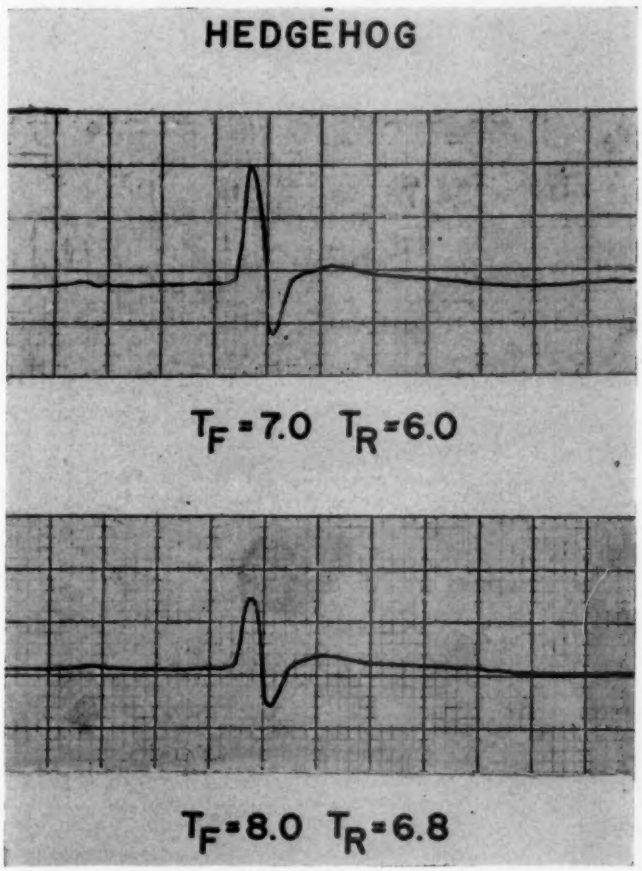

Fig. 9—Representative electrocardiograms of hedgehog in deep hibernation. T_F = front skin temperature. T_R = rear skin temperature. Ten heavy lines horizontally = 1 second. Two heavy lines vertically = 1 mv.

S values differed from component to component as they were evaluated, from one ECG to another. In all the ECGs studied, the per cent of cases at the five different S values were plotted graphically for each of the five components (Fig. 11). It is clearly demonstrated here that the P-R undergoes in most cases the greatest amount of stretch, that the QRS in most cases is stretched next most, and P and Q-T next in order, and that the RS-T in most cases undergoes the least amount of stretch or extension.

In view of the fact that (excepting the T-P interval) the P-R interval underwent the greatest extension, a further analysis of P-R extension was in order. The time intervals occupied by P-R under conditions of anesthesia and conditions of hibernation were plotted with respect to the body temperatures of the three species of animals (Figs. 12, 13, 14). It can be seen from the graphs that as body temperature falls, the P-R interval lengthens, and there is a large disproportionate lengthening of the P-R at body-temperature values below 10° C.

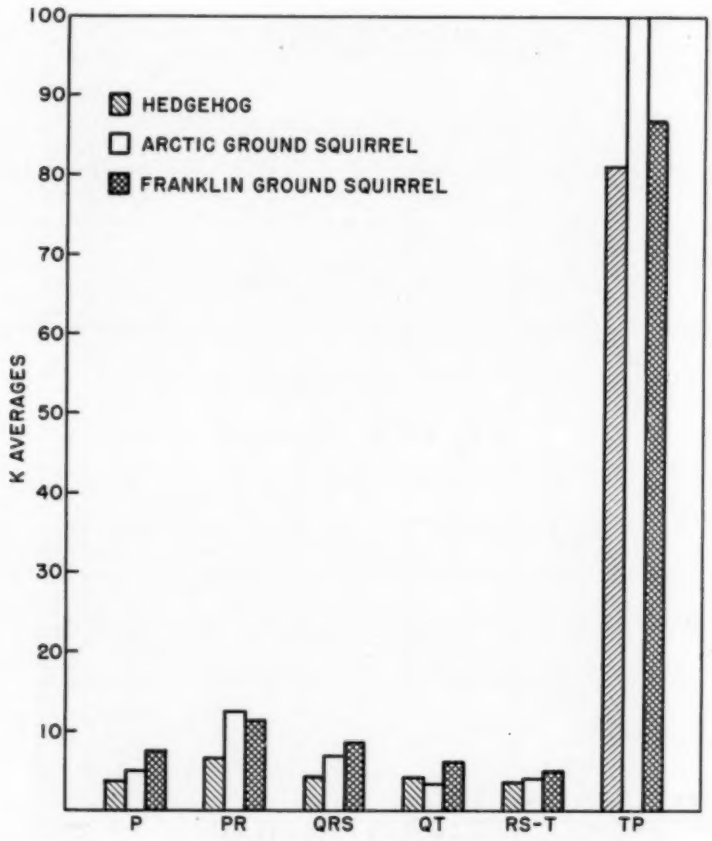

Fig. 10.—$K = \frac{\text{time interval in the hibernating heart in seconds}}{\text{time interval in the Nembutalized heart in seconds}}$

K therefore is the measure of "stretch" or extension of the ECG component as a comparison between the normal anesthetized condition and the hibernating condition. K averages were obtained from the following numbers of ECGS: (1) hedgehog—17 ECGS in anesthesia, 11 ECGS in hibernation; (2) Arctic ground squirrel—6 ECGS in anesthesia, 7 ECGS in hibernation; (3) Franklin ground squirrel—10 ECGS in anesthesia, 6 ECGS in hibernation.

DISCUSSION

Rasmussen[15] cites Gessner[16] (1551) as the first person in the modern era to be experimentally interested in the physiology of hibernation. Many theories and historical facts with respect to hibernation have been well summarized by Rasmussen.

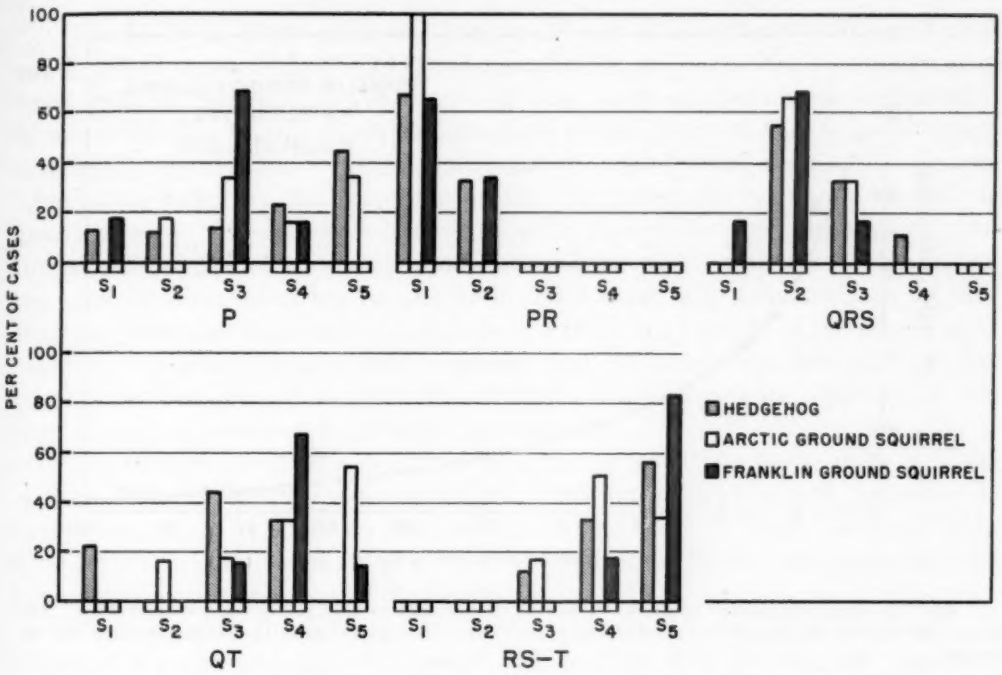

Fig. 11.—K values for the components of each electrocardiogram are arranged by order of "magnitude of stretch" factor, designated S_1 for greatest magnitude of stretch or extension, S_2 for next most stretched component, then S_3, S_4, and finally S_5 which indicates least magnitude of stretch or extension. The distribution of the "stretch magnitudes" are shown for each component. It can be seen that the P-R component is stretched most in all three species, and that the RS-T component is stretched least in two species.

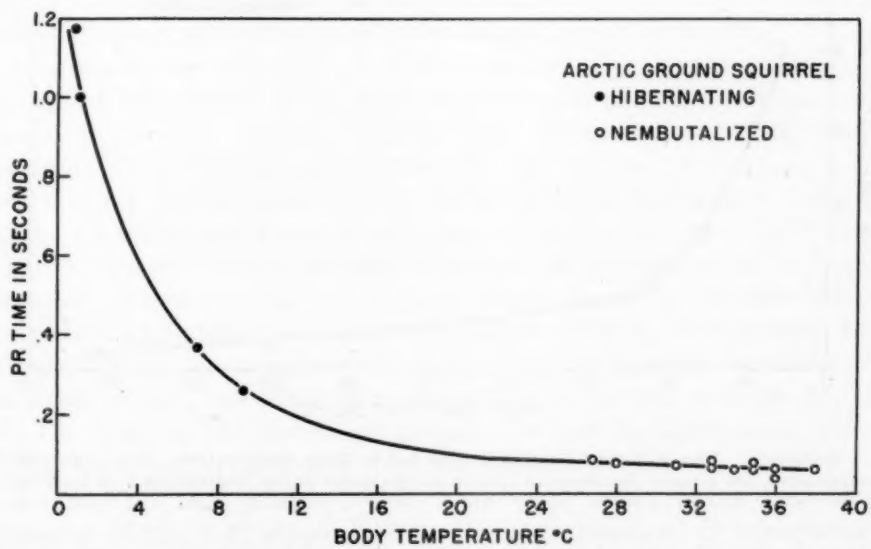

Fig. 12.—Arctic ground squirrel. The P-R time lengthens with fall in body temperature. The lower the body temperature, the greater the observed increment of change in the lengthening P-R interval.

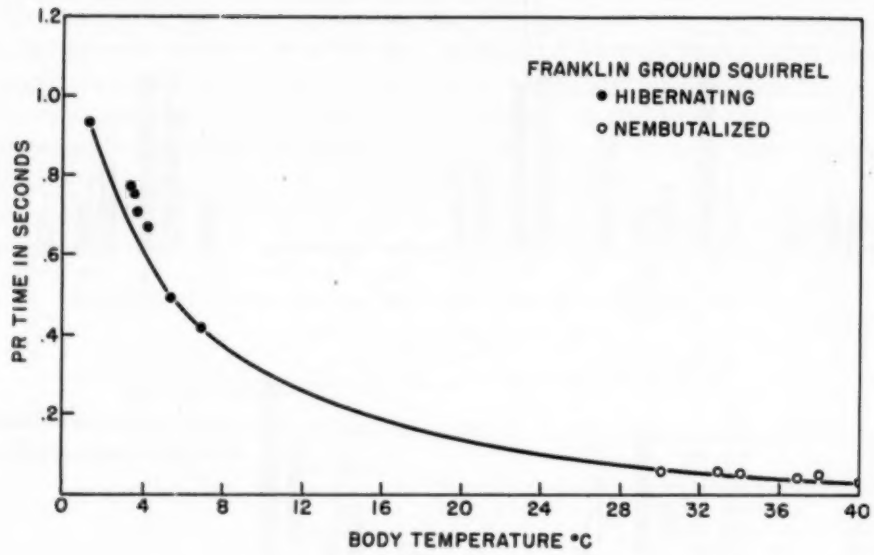

Fig. 13.—Franklin ground squirrel. The P-R time lengthens with fall in body temperature. The lower the body temperature the greater the observed increment of change in the lengthening P-R interval.

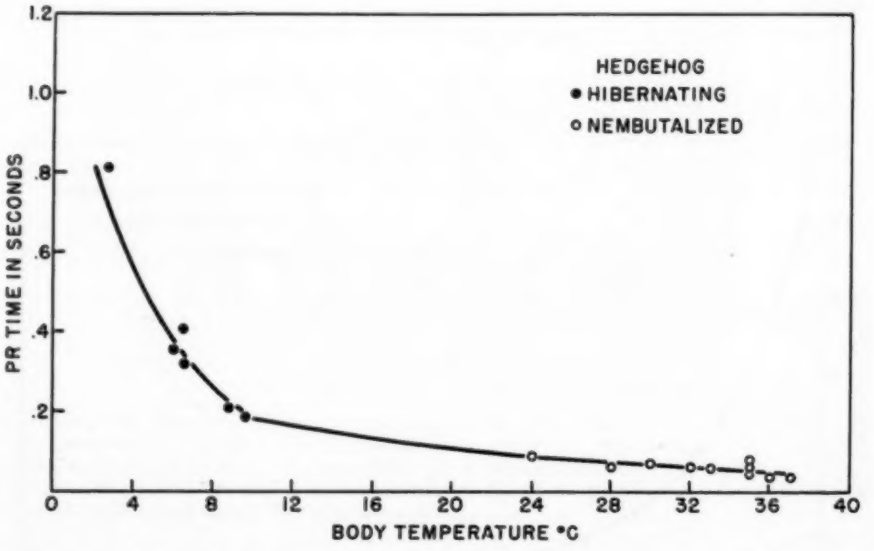

Fig. 14.—Hedgehog. The P-R time lengthens with fall in body temperature. The lower the body temperature, the greater the observed increment of change in the lengthening P-R interval.

The heart in hibernation has been a subject of investigation for well over one hundred years. Hall[17] (1832) enunciated the fact that the continuation of heart beat in hibernation (at extremely low body temperatures) indicated a hyperexcitability of this heart as compared to the heart of the nonhibernating mammal. Merzbacher[18] in 1904 stimulated interest and speculation in the hibernating heart by showing that hibernating hearts of mammals as well as hearts of other hibernating vertebrates, such as reptiles and amphibians, continued to beat for many hours after decapitation of the animals. The fact of the extreme slowness of the heart rate in hibernation was demonstrated by Du Bois[19] in 1896 who reported a heart rate of 3 beats per minute in the hibernating marmot. Johnson[12] later (1928) reported that the maximum heart rate of the normal 13-lined ground squirrel was 80 times the slowest rate observed in the same animal in hibernation (5 beats per minute).

The slowest recorded rate of the hibernating heart has been given by Tait[2] as 2 beats per minute in the woodchuck. His paper is indefinite, however, as to whether or not this was an *isolated* hibernating heart. Chao, Iping and Yeh[7] have reported that the heart beat of a hibernating hedgehog was imperceptible except by direct inspection of the heart.

The fact that the hibernating animal enters, remains, and comes out of hibernation every few days in a more or less cyclic fashion was first observed and reported upon by Hall.[17] Horvath[20] studied this phenomenon in the ground squirrel and noted in the animals he studied that the periods of torpor did not exceed 15 days. He noted, furthermore, that the times *in* hibernation became longer as the hibernation season continued.

Capillary electrometer records of the hibernating hearts of the bat, dormouse, and hedgehog were obtained by Buchanan[21,22] in 1911. Electrocardiograms on hibernating ground squirrels have been taken by Johnson.[23] Barcroft[24] recorded electrocardiograms of the hibernating marmot. Chatfield and Lyman[25] obtained ECGs of the golden hamster on arousal from hibernation.

Changes in the durations of components of electrocardiograms as a consequence of hibernation have been reported by several investigators. For example, Buchanan[21] reported a dissociation between auricles and ventricles in hibernation in the dormouse. She also reported a dropping out of the P wave. Endres and associates[13] have indicated that arrhythmias occur during arousal. Chatfield and Lyman[25] show that P-R durations and QRS durations shorten on arousal. Barcroft[24] also reports a loss of the P wave in the deeply hibernating animal. Crismon,[5] studying hypothermia of nonhibernating rats down to lethal temperatures (body temperature close to 16° C.) found that the P-R and QRS intervals lengthen with cold. He also observed an atrioventricular dissociation at very low temperatures which he correlated with low blood pressure. He believed the low blood pressure in turn brought about an anoxic condition at the heart, eventually resulting in heart block.

We have not seen total heart block, although we do report the remarkable lengthening of the P-R interval at the low temperatures of hibernation. In several instances we have observed the loss of the P wave. In view of the fact, however, that the P wave is of extremely low voltage and yet of very long duration

in the ECG of the hibernating animal, it is believed that such observations may in fact represent limits of response of the recording mechanism. Use of a D. C. amplifier would be necessary to record slow low voltage waves such as this P wave, in order to clarify this problem. The observed loss of a P wave in hibernation awaits, therefore, corroboration or disproof by the use of D. C. equipment.

The tremendous extension of the T-P interval in hibernation indicates clearly that the primary method whereby the hibernating heart attains its low heart rate values is by a decrease in the automaticity of the SA node. This fact was attested to by Hoy[26] (1875) who noted that the hibernating heart exposed in the opened chest of the ground squirrel beat at a rate of 4 per minute but that the actual movement of the heart occupied 4 seconds in each beat.

The P-R interval shows lengthening due to hibernation second only to the T-P interval. It is thus valid to say that the conduction time of the heart is slowed greatly by hibernation, but not slowed as much as the automaticity of the SA node.

Lastly, in view of the fact that the RS-T represents repolarization time of the ventricles, it is correct to state that the repolarization time of the ventricles is least affected by hibernation. If the RS-T time is considered as a function of body temperature, this proposition can be restated as follows: the RS-T remains relatively unchanged by body temperature change. From a physical-chemical standpoint, electrolytic reactions occurring at very small electrodes or points behave in this fashion. It may well be, therefore, that the RS-T segment reflects an electrolytic process at the cellular level.

SUMMARY

1. The hearts of the hibernating hedgehog, Arctic ground squirrel, and Franklin ground squirrel have been studied electrocardiographically.

2. Heart rate: (a) Heart rates are best described during the periods when animals are *going into*, *in*, and *coming out* of hibernation. Heart rate can in these periods be shown with reference to time and body temperature. With reference to time they are cyclic in periods of several days. With reference to temperature the function is different going into hibernation than it is coming out of hibernation. (b) *Going into* hibernation the heart shows a hyperirritability beginning at a body temperature of about 20° C., which precludes heart standstill as it would occur in most other mammals on cooling. *In* deep hibernation the heart rate is greatly slowed to values as low as 2.2 beats per minute but stabilizes at body temperatures somewhat above ambient temperatures, on an average 2.1° C. above ambient temperatures in the three species. The heart rate may show unusual patterns such as pairing of beats or beats in bursts. *Coming out* of hibernation the rise in heart rate precedes the rise in body temperature.

3. Electrocardiograms: (a) Since the heart rates have descended to very low values, the components of the electrocardiograms *in* deep hibernation in all three species have been greatly stretched or extended by comparison to the

components of nonhibernating lightly anesthetized animals of the same species. The stretch or extension of these components is of the following order of magnitude:

(1) The T-P interval is lengthened far and beyond all other components. That is, the automaticity of the SA node is most particularly slowed in hibernation.

(2) The P-R interval is lengthened next most. That is, the conduction time is increased next most.

(3) The QRS interval, P interval, and Q-T interval are in decreasing order. The RS-T interval shows the least amount of extension or stretch due to hibernation. If this is strictly representative of a temperature effect, it may be an indication that the RS-T reflects the time of a cellular electrolytic reaction. It is reasonable that the Q-T stretch be intermediate in value between the QRS and RS-T since it is largely composed of these two intervals.

(b) Although complete heart block was not observed, a marked lengthening of the P-R interval (conduction time of the heart) does occur, primarily at hibernating body temperatures below 10° C.

SUMMARIO IN INTERLINGUA

Esseva studiate electrocardiographicamente le cordes de hibernante individuos de *Erinaceus*, *Citellus parryi*, e *C. franklini*. Al initiar del hibernation, a un temperatura corporee de circa 20 C., le pulsation del corde es hyperirritabile. In profunde hibernation illo es reducite usque a 2,2 pulsos per minuta e se stabilisa a un temperatura corporee de circa 2,1 C. supra illo del ambiente. Al emerger del hibernation, le pulsation del corde se accelera ante que le temperatura corporee comencia crescer.

Le componentes temporal del electrocardiogramma in hibernation es grandemente extendite in comparation con le componentes temporal de electrocardiogrammas ab animales levemente anesthesiate. Secunde lor magnitude iste extensiones se presenta in le sequente ordine: T-P, P-R, QRS, P, Q-T, e RS-T. Le plus grande extension de P-R occurre a temperaturas corporee infra 10 C. Interessante implicationes theoric es trovabile in le facto que le componente RS-T manifesta su minimo de extension in le frigide corpore animal.

Many of the techniques with respect to induction and maintenance of animals in hibernation as described herein were developed and put into effect by Dr. Fred A. Ryser, Jr. who was particularly concerned with metabolic aspects of hibernation as they related to temperature.

Three University of Wisconsin undergraduate students devoted hundreds of hours in tabulating the data from the long hibernation experiments. It is well that they be mentioned for their devotion and patience. They are Miss Helen Wiechman, Miss Marilyn Johnson, and Mr Donald Belleau.

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ACUTE PULMONARY INFECTION AND CARDIAC FAILURE IN CHRONIC EMPHYSEMA*

K. BRAUN, M.D., AND G. IZAK, M.D.

JERUSALEM, ISRAEL

IN a group of patients suffering from pulmonary emphysema and chronic bronchitis, heart failure may be precipitated by acute pulmonary infection.[1-4] In such patients, alterations in the pulmonary circulation are functional and reversible in nature. These patients tend to recover from heart failure following resolution of the infection. This clinical course is distinctly different from the progressive cardiac insufficienty which results from structural reduction in the pulmonary circulation due to chronic inflammation, fibrosis, carcinosis, silicosis, or other pneumoconioses.

The following report describes clinical and laboratory observations in seven patients in whom acute pulmonary infection was found to be responsible for the development of congestive heart failure.

METHODS

During the period of observation serial pulmonary function tests were performed. Vital capacity and maximum breathing capacity were measured by the spirographic technique.[5] The predicted vital capacity and maximum breathing capacity were determined by the formulas of Baldwin and associates.[6] Arterial blood was collected by the technique of Riley and associates[7] using heparin to prevent clotting and a small globule of mercury in the serum for mixing. Arterial blood gases were determined by the method of Van Slyke and Neill.[8] In two cases blood pH was determined with the Cambridge pH meter,[9] and the pCO_2 of the arterial blood was calculated from the carbon dioxide content and the pH, utilizing the nomograms of Singer and Hastings.[10] Cardiac catheterization was performed in two cases by the Cournand technique.[11] Venous pressure was measured by the direct method of Moritz and Tabora and the arm-to-tongue circulation time was determined with Decholin.

SUMMARY OF CASE REPORTS

The seven patients included in this study ranged in age from 29 to 65 years; two of them were females and five were males. They showed many common

From the Cardiovascular Research Laboratory and Department of Internal Medicine 'B', Rothschild Hadassah University Hospital, Jerusalem, Israel.

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features with regard to their past histories and present illnesses. They had suffered from spastic bronchitis with chronic cough, dyspnea, nonbloody sputum, and frequent bouts of fever over a period of from 4 to 8 years. All were hospitalized because of increased cough, fever, dyspnea, palpitation, and peripheral edema.

At the time of admission, physical examination revealed many findings common to all of the patients. They were severely dyspneic, with orthopnea and tachypnea, and extremely cyanotic (Grade 3-4). Their temperatures were between 37.8°C. and 39°C. The pulse rate was regular and about 120 per minute, and the blood pressure was within normal limits. The neck veins were distended. The chest was barrel-shaped, and the respiratory movements were diminished. In four of the patients there was marked clubbing of the fingers. The percussion note in all cases was hyperresonant, and on auscultation, moist râles and sibilant rhonchi were heard all over the lungs. The heart was enlarged to percussion in all directions, and the second pulmonic sound was accentuated. The liver was markedly enlarged, and the edge was smooth and tender. In one case there were signs of ascites. There was marked peritibial edema (2 to 3-plus) in all patients.

TABLE I. SUMMARY OF LABORATORY DATA IN SEVEN CASES

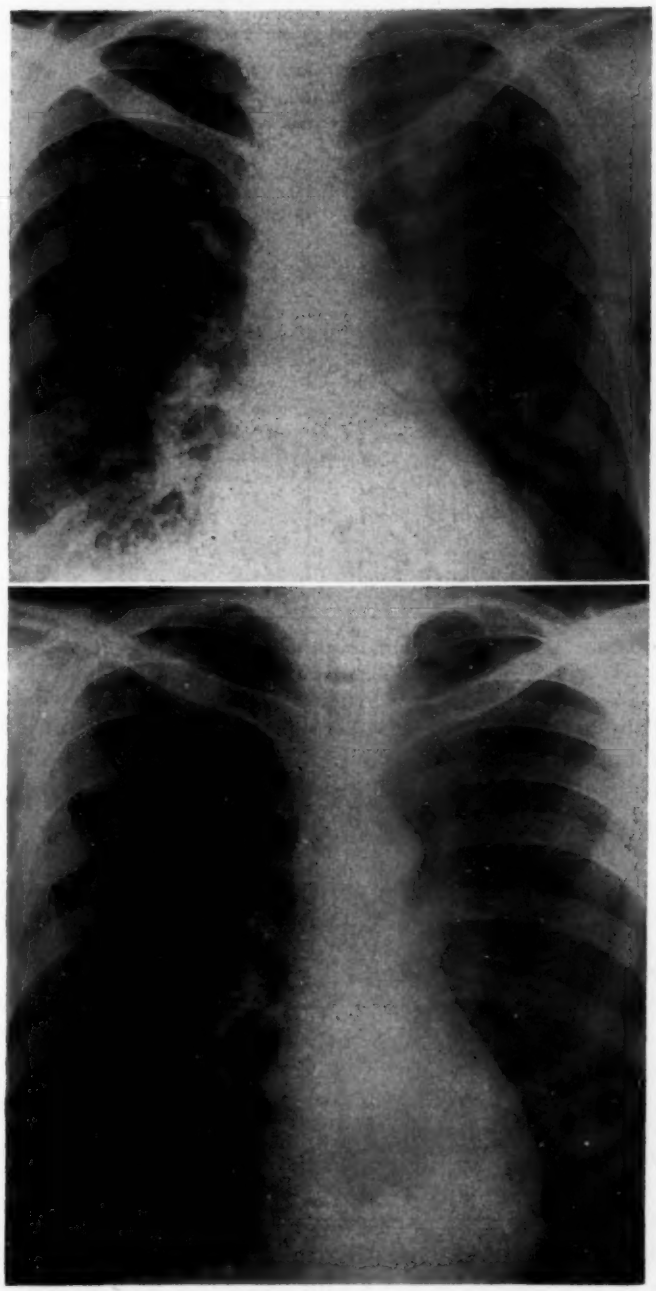
NO.	NAME	AGE	SEX	SED. RATE WESTERGREN (MM.)	HB. (GM. %)	RED BLOOD COUNT (ML./MM.^{3})	HEMATOCRIT (%)	WHITE BLOOD COUNT (MM.^{3})	URINE	BLOOD CHEMISTRY
1	M.Z.	46	M	2/3	15.0	6.8	60	18,100	Neg.	Normal
2	K.M.	35	M	5/20	14.0	5.1	50	10,000	Alb.+ RBC+	Alb. 2.5 Glob. 3.7 gram %
3	P.S.	29	F	1/2	17.0	6.9	72	15,400	Neg.	Normal
4	L.J.	54	M	2/4	17.0	6.0	66	8,900	Neg.	Normal
5	K.M.	65	M	5/11	14.0	4.9	52	24,400	Alb.+	Urea 52 mg. %
6	T.A.	68	M	2/6	17.5	5.8	60	17,600	Neg.	Normal
7	A.E.	50	F	10/22	12.3	4.5	48	12,500	Neg.	Normal

The significant laboratory findings are summarized in Table I. Chest x-rays taken at the time of admission showed a similar picture in all cases. There was increase in the cardiac shadows, dilatation of the pulmonary artery, and increased hilar markings. In addition, there were densities in the right lower lung field suggesting bronchopneumonia (Fig. 1,*A*). Electrocardiograms showed right ventricular strain and tall peaked P waves (P pulmonale).

At the time of admission the venous pressure ranged from 20 to 29 cm. of water and the circulation time from 18 to 24 seconds.

Serial pulmonary function tests and arterial blood gas studies were performed during the course of the disease. At the time of admission they showed a markedly decreased vital capacity and maximum breathing capacity, arterial oxygen unsaturation, and in six cases retention of carbon dioxide. Table II summarizes

A.



B.

Fig. 1.—*A*, Chest x-ray of patient K.M. (Case 2) at admission shows diffuse enlargement of the heart, increased hilar markings, and density in the right lung field. *B*, Chest x-ray 15 days later shows a diminution in the heart size and disappearance of the density in the right lung field.

TABLE II. SUMMARY OF PULMONARY FUNCTION TESTS AND VENOUS PRESSURE VALUES BEFORE AND AFTER RECOVERY

NO.	NAME	AGE	SEX	DATE	V.C. (% OF PRED.)	M.B.C. (% OF PRED.)	O_2 SAT. (%)	CO_2 CONT. (VOL. %)	VEN. PRESS. CM. WATER
1	M.Z.	46	M	10/27/52	21	13	55	61.32	22.5
				6/10/52	33	19	85	57.77	6.5
2	K.M.	35	M	7/27/52	48	23	71	51.04	28
				7/31/52	97	71	86	49.57	13
3	P.S.	29	F	1/27/52	43	37	55	47.23	29
				2/ 1/52	63	59	86	48.50	14
4	L.J.	54	M	6/15/52	36	19	48	60.75	29
				7/ 6/52	70	26	91	58.44	14
5	K.M.	65	M	12/17/52	30	16	71	66.32	22
				1/ 7/53	50	39	90	46.39	13
6	T.A.	68	M	1/14/54	24	—	77	70.13	20
				2/10/54	67	—	94	52.33	12
7	A.E.	50	F	3/ 7/54	33	—	57	63.80	24
				4/20/54	69	—	88	48.50	12

V.C.=Vital capacity; M.B.C.=Maximum breathing capacity; % of Pred.=Per cent of prediction.

the results obtained at admission and following recovery from congestive heart failure. Cardiac catheterization was performed in patient No. 3 at the time of admission and in patient No. 5 following recovery from heart failure. Results obtained are given here.

	Pulm. art. press. (mm. Hg)	*Cardiac output* (L./min.)	*Cardiac index* (L./m.²/min.)
Case 3 (before O_2)	135/45	6.35	4.75
Case 3 (after O_2)	93/20		
Case 5	30/8	4.9	2.9

Treatment consisted of a low-sodium diet, intermittent oxygen breathing, and injections of penicillin, streptomycin, or administration of Aureomycin, as indicated by the in vitro sensitivity of the microorganisms cultured from the sputum. Xanthine preparations were given parenterally or per os and epinephrine by inhalation. In three cases digitalis and mercurial diuretics were used and in three others adrenocorticotrophic hormone was administered after the signs of congestive heart failure had disappeared. The period of observation and treatment lasted between 12 and 44 days.

In all cases there was steady but gradual improvement in the condition of the patients as manifested by the decrease in signs of cardiac failure, which paralleled the resolution of the pulmonary infection. The results of the pulmonary

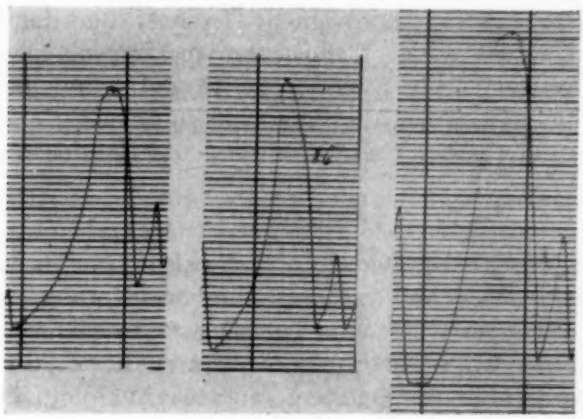


Fig. 2.—Spirograms recorded during the course of the disease in patient T.A. (Case 6) shows markedly reduced vital capacity and prolongation of the expiratory slope at admission. With recovery from the pulmonary infection the vital capacity gradually increases but the expiratory slope is still prolonged indicating obstructive emphysema.

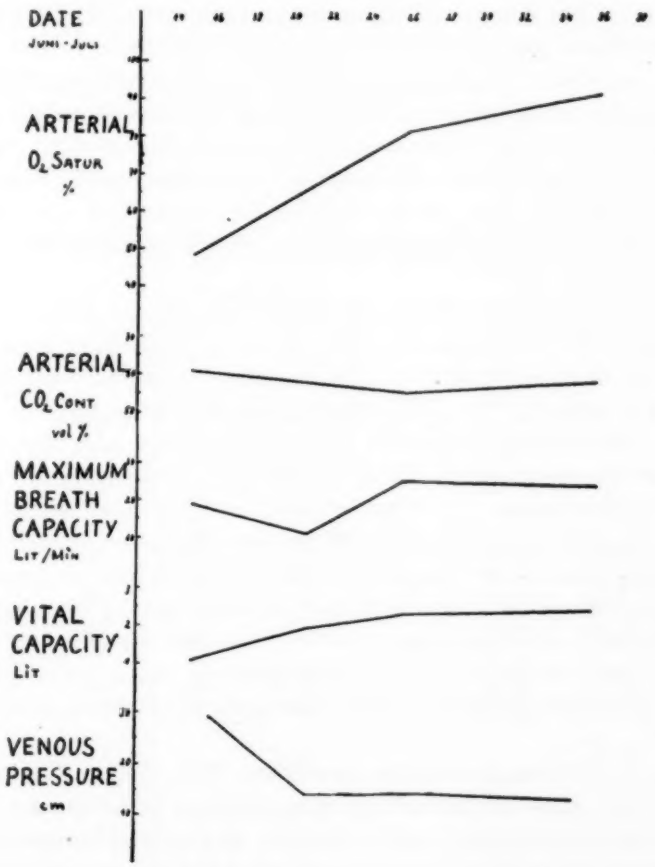


Fig. 3.—Note the decrease of the venous pressure coinciding with the improvement in the pulmonary functions.

function tests indicated marked improvement (Table II) and the venous pressure approached normal values. Fig. 2 illustrates the improvement of the vital capacity with the recovery. Fig. 3 shows the drop of venous pressure as being closely related to the improvement in pulmonary functions (Case 4). Repeated x-rays showed return of the heart size to normal and clearing of the lung fields (Fig. 1,*B*).

DISCUSSION

From the data presented previously, it is evident that marked ventilatory and respiratory insufficiency and cardiac failure were present at the time of admission. Acute pulmonary infection superimposed on chronic lung disease was apparently responsible for the development of cardiac failure in these seven patients. The development of congestive failure in cor pulmonale is thought to be related to an increase in pulmonary artery pressure.[12-15] That this pulmonary hypertension may be reversible was demonstrated by catheterization in one of our cases (Case 5) whose pulmonary artery pressure was found to be normal after recovery from severe heart failure. Similar observations have been made by Harvey and associates[15] and Mounsey and associates.[4]

A number of factors may account for the development of pulmonary hypertension and heart failure in this group of patients. Decrease in the functioning pulmonary parenchyma by bronchopneumonia may have reduced the pulmonary vascular bed causing increased resistance in the pulmonary circulation. Our examinations revealed in each case a significant decrease in vital capacity and maximum breathing capacity at the time of congestive heart failure. These observations are different from those of Whitaker[14] who did not find any significant decrease in the ventilatory functions in similar patients with congestive heart failure.

Another factor affecting pulmonary pressure is anoxia which was marked in all of our cases. It has repeatedly been shown in man that anoxia produces a significant increase in pulmonary artery pressure apparently by direct action on the pulmonary vessels.[17-20] This effect is more pronounced in patients in whom there is a pre-existing reduction of the pulmonary vascular bed, as was probably the case in our patients. The beneficial effect of oxygen breathing on the pulmonary hypertension was demonstrated in Case 3 in which pulmonary artery pressure dropped from 134/45 to 95/24 mm. Hg after oxygen administration. Other consequences of anoxia include hypervolemia, increased cardiac output, and polycythemia.[21] The first two of these factors increase the blood volume in the pulmonary circulation and limit further the capacity of the pulmonary vascular bed. Polycythemia, by increasing the blood viscosity, augments the pulmonary vascular resistance, thus raising further the pulmonary artery pressure.

Yu and associates[15] suggested the possibility that carbon dioxide retention is a more important cause of pulmonary hypertension than anoxia. This view is supported by the investigations of Whitaker.[14] Both authors found a very good correlation between the carbon dioxide content of the mixed venous blood and the mean pulmonary artery pressure. Another important factor is fever, which by increasing the metabolic rate brings about a rise in oxygen consumption and

in cardiac output. All these various mechanisms combine to produce an abnormal rise in pulmonary artery pressure. Right ventricular dilatation and cardiac failure result when the hypertrophied, anoxic right ventricle is no longer capable of coping with the increased pulmonary resistance and the demand for increased cardiac output.[13]

In this group of patients with chronic emphysema the clinical picture may be complicated by respiratory acidosis which results from carbon dioxide retention.[1,23,24] Mental symptoms such as confusion and stupor are frequently present. These signs are often attributed to cerebral anoxia and are treated with inhalation of oxygen. However, this therapy may result in further deterioration of the mental state and even in coma.[22-24] The mechanism responsible for this sequence of events is now well understood. The regulation of respiration during marked hypercapnia is no longer controlled by stimulation of the respiratory center by CO_2; the prolonged high levels of carbon dioxide in the blood "poison" the respiratory center so that the main stimulus to breathing becomes anoxia which operates through the carotid sinus and the aortic chemoreceptors. Relief of anoxia by administration of oxygen removes this respiratory stimulus and causes a decrease in ventilation which in turn increases further the carbon dioxide retention thereby leading to respiratory acidosis. This course of events was demonstrated in Cases 6 and 7 in which mental disturbances, hypoventilation, apnea, and increased pCO_2 were observed even after short exposure to high oxygen concentrations (Table III). Hypoventilation under such circumstances can be avoided by applying artificial respiration with the aid of a respirator.[24]

TABLE III. CHANGES IN pCO_2 FOLLOWING SHORT EXPOSURE TO CONCENTRATED O_2 AT VARIOUS STAGES OF THE DISEASE IN CASES 6 AND 7

NO.	DATE	pCO_2 MM. HG		pH		O_2 CONT. VOL. %		CO_2 CONT. VOL. %	
		RESTING	AFTER 10 MIN. O_2 BREATH.	RESTING	AFTER 10 MIN. O_2 BREATH.	RESTING	10 MIN. O_2 BREATH.	RESTING	AFTER 10 MIN. O_2 BREATH.
6	1/14/54	61	76	7.45	7.37	16.38	26.13	59.90	64.21
	1/19/54	56	69	7.4	7.31				
	1/21/54	55	53	7.44	7.46	22.18	25.35	65.09	64.68
	1/28/54	65	116	7.4	7.2	21.06	24.88	70.20	75.75
	2/ 2/54	48	48	7.47	7.47	18.27	22.37	59.87	59.83
7	3/ 7/54	56	62	7.4	7.37	10.30	18.38	63.80	65.27
	3/ 9/54	47	60	7.42	7.33	12.27	17.15	55.36	60.75
	3/14/54	48	62	7.39	7.31	11.42	15.62	54.03	57.55
	4/ 4/54	34	34	7.55	7.51	15.51	16.91	51.27	51.41

The therapy of this condition includes the control of the infection by the use of broad spectrum antibiotics and intensive treatment with bronchodilators such as aminophylline and epinephrine aerosol. In some cases it may be advisable to use small amounts of ACTH to achieve effective bronchodilatation.[25,26] It may also be necessary to remove excessive bronchial secretions by pharyngeal

or tracheal aspiration, especially when the patient is in a state of stupor. Pneumoperitoneum has been recommended for treatment of carbon dioxide retention.[1] We have used it in one case but without beneficial effect. Digitalis preparations are generally used, but their effectiveness is extremely difficult to evaluate in this type of reversible heart failure.

SUMMARY

Seven patients with chronic pulmonary disease, in whom heart failure was precipitated by acute pulmonary infection, are reported. There was a close correlation between the degree of pulmonary insufficiency and the severity of congestive heart failure. Recovery from the acute pulmonary infection was followed by the disappearance of the signs of cardiac failure. The therapy of this condition is outlined. In two cases, breathing of concentrated oxygen increased respiratory acidosis. The mechanism of this harmful effect of oxygen therapy is discussed.

SUMMARIO IN INTERLINGUA

Es reportate 7 casos de patientes con chronic morbo pulmonar in qui dysfunctionamento cardiac esseva precipitate per acute infection pulmonar. Esseva constatate un clar correlation inter le grado de insufficientia pulmonar e le severitate de dysfunctionamento cardiac congestive. Le recuperation ab le acute infection pulmonar esseva sequite per le disparition del signos de dysfunctionamento cardiac. Es presentate le lineas general del therapia pro iste condition. In duo casos le inhalation de oxygeno concentrate augmentava le acidosis respiratori. Es discutite le mechanismo de iste effecto nocive del therapia a oxygeno.

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A CLINICAL EVALUATION OF THE SURGICAL MANAGEMENT OF COMBINED MITRAL AND AORTIC STENOSIS

WILLIAM LIKOFF, M.D.,* DONALD BERKOWITZ, M.D.,** CLARENCE DENTON, M.D.,*** AND HARRY GOLDBERG, M.D.****

PHILADELPHIA, PA.

COMBINED commissurotomy for mitral and aortic stenosis is a natural outgrowth of the development and independent use of these surgical techniques in rheumatic heart disease. The present study was undertaken to review the clinical results of this operation in seventy-four patients and to establish criteria for multivalvular surgery.

MATERIAL

The seventy-four patients consisted of twenty-nine males and forty-five females ranging in age from twenty-two to fifty-nine years. They were divided into the following groups (Table I).

Group 1 consisted of eleven patients with significant aortic and mitral stenosis, uncomplicated by other lesions.

Group 2 consisted of thirty-nine patients in whom major aortic and mitral stenosis was accompanied by additional insignificant valve lesions.

Group 3 consisted of twenty-four patients in whom aortic and mitral stenosis was accompanied by additional significant valve lesions.

Specific criteria have been established for the differentiation of significant and insignificant valve involvement.[1]

Status Prior to Operation (Table II).—Uncomplicated aortic and mitral stenosis occurred predominantly in the female. When combined stenosis was associated with additional insignificant lesions the ratio did not change, but in Group 3 more males were encountered than females. The majority of the patients offered a positive history of rheumatic activity.

From the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic, Philadelphia, Pa.

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*Associate Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

**Former Chief Resident in Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.: Present address: Dept. of Medicine, Temple University Hospital, Philadelphia, Pa.

***Instructor in Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

****Assistant Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

TABLE I. DIAGNOSES IN 74 CASES OF RHEUMATIC HEART DISEASE UNDERGOING MULTIVALVULAR SURGERY

GROUP	DIAGNOSIS	NO.	DEATHS	MORTALITY (%)
1	AS, MS	11	—	—
2	AS, MS, ai	18	3	16.6
	AS, MS, mi	4	—	—
	AS, MS, ai, mi	17	5	29.4
	Totals	39	8	20.5
3	AS, MS, MI	4	—	—
	AS, MS, AI	3	1	33.3
	AS, MS, MI, ai	1	—	—
	AS, MS, AI, mi	4	4	100.0
	AS, MS, AI, MI	4	2	50.0
	AS, MS, TS, ai	2	—	—
	AS, MS, AI, TS, mi	2	2	100.0
	AS, MS, TS	1	1	100.0
	AS, MS, TS, mi, ai	1	1	100.0
	AS, MS, AI, TS	1	1	100.0
	AS, MS, MI, TS, ai	1	—	—
	Totals	24	12	50.0
	Over-all totals	74	20	27.0

Capital letters indicate significant lesions.

AS = Aortic stenosis; MS = Mitral stenosis; AI = Aortic insufficiency; MI = Mitral insufficiency; TS = Tricupid stenosis.

Easy fatigability was present in all patients. Dyspnea of varying degrees was also a primary and universal symptom. In 84 per cent it had been present for more than two years. The paroxysmal form with pulmonary edema occurred in 42 per cent but was observed only in those who had complained of dyspnea for at least two years. Peripheral edema occurred in at least one-half of the patients of each group and in 58 per cent of the total. Ascites was encountered in 16 per cent, but only in patients with peripheral edema. Recurrent hemoptysis was reported by 34 per cent. Angina, vertigo, and syncope occurred in that order of frequency, and each was observed in less than 25 per cent of the patients. When first seen, 50 per cent of the patients had various manifestations of congestive heart failure.

Physical Findings on Admission.—Atrial fibrillation was the dominant rhythm in 58 per cent of the patients. Embolic accidents had occurred in 24 per cent of the total group and only in those who had atrial fibrillation. This complication was most frequent in Group 2.

The blood pressure levels were normal in 81 per cent of the patients. The rough systolic murmur of aortic stenosis was consistently present, and in 87 per cent was associated with a diminished or absent aortic second sound. A

TABLE II. SUMMARY OF PREOPERATIVE DATA

	GROUP 1 (11)		GROUP 2 (39)		GROUP 3 (24)		TOTALS	
	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Male	2	18	14	36	13	54	29	39
Female	9	82	25	64	11	46	45	61
History of rheumatic fever	5	46	35	89	20	83	60	81
Fatigue	11	100	39	100	24	100	74	100
Dyspnea								
Less than 1 yr.	2	18	5	13	5	21	12	16
2 to 5 yr.	7	64	16	41	14	58	37	50
More than 5 yr.	2	18	18	46	5	21	25	34
Pulmonary edema	4	36	20	51	7	29	31	42
Angina	1	9	11	28	6	25	18	24
Syncope	—	—	5	13	3	13	8	11
Vertigo	1	9	9	23	5	21	15	20
Edema	7	64	24	62	12	50	43	58
Ascites	1	9	8	21	3	13	12	16
Hemoptysis	3	27	14	36	11	46	28	34
Emboli	1	9	13	33	4	17	18	24
Rhythm								
Atrial fibrillation	6	54	22	56	15	62	43	58
Normal sinus rhythm	5	46	17	44	9	38	31	42
Failure on admission	5	46	21	54	11	46	37	50
Blood pressure								
Normal	8	73	34	87	18	75	60	81
Systolic over 150	1	9	3	8	2	8	6	8
Systolic below 100	2	18	2	5	4	17	8	11
A_2								
Normal	2	18	5	13	3	13	10	13
Decreased	9	82	34	87	21	87	64	87
Thrill (aortic area)	5	46	30	77	17	71	52	70
Heart size								
Normal	4	36	3	8	—	—	7	10
1-plus	2	18	3	8	2	8	7	10
2-plus	5	46	15	38	12	50	32	44
3-plus	—	—	18	46	9	38	27	36
4-plus	—	—	—	—	1	4	1	1

systolic thrill located at the base of the heart was palpable in 70 per cent. Without exception, the mitral first sound was abnormally short and high-pitched. A mitral diastolic murmur was heard in all the patients. A moderately intense blowing mitral systolic murmur, not transmitted from the aortic area, was heard in nine patients who later did not prove to have an associated mitral regurgitation.

A comparison of heart size in the three groups of patients revealed no enlargement greater than Grade 2 in uncomplicated mitral and aortic stenosis, and enlargements beyond this degree in over 40 per cent of the patients classified in Groups 2 and 3. Calcification of the aortic or mitral valve was observed in 55 per cent of the total group.

The electrocardiogram was abnormal in all but six patients (Table III). The three most frequent abnormalities consisted of right or left ventricular hypertrophy, and atrial fibrillation. At least one of these patterns was found

in 75 per cent of the abnormal tracings. Interventricular conduction defects and evidence of coronary artery disease were observed only in isolated instances.

TABLE III. ELECTROCARDIOGRAMS IN 74 CASES OF MULTIVALVULAR SURGERY

	GROUP 1	GROUP 2	GROUP 3	TOTALS
				(%)
Normal	1	4	1	6 (8)
Right ventricular hypertrophy and strain	5	8	4	17 (23)
Atrial dysfunction	2	2	1	5 (7)
Left ventricular hypertrophy and strain	1	11	5	17 (23)
First degree heart block	—	2	2	4 (6)
Left ventricular hypertrophy with atrial dysfunction	—	1	1	2 (3)
Left and right ventricular hypertrophy and strain	—	1	3	4 (6)
Coronary artery disease	—	1	—	1 (1)
Left bundle branch block	—	—	1	1 (1)
Atrial fibrillation, otherwise normal	2	9	6	17 (23)

In all of the patients in whom a brachial artery tracing was recorded, an anacrotic notch or slurring of the ascending limb of the curve with a delay in its peak was observed. Either of these abnormalities is considered diagnostic of aortic stenosis.

RESULTS

Operative Mortality (Table I).—There were twenty deaths in the entire group for a mortality of 27.0 per cent. There were no deaths among the eleven patients in Group 1, eight deaths (20.5 per cent) in Group 2, and twelve deaths (50.0 per cent) in Group 3. The presence of an additional insignificant aortic insufficiency greatly increased the mortality. An accompanying significant aortic insufficiency was attended by the highest mortality figures with ten deaths occurring in fourteen patients (71.4 per cent).

The presence of an associated mitral insufficiency, insignificant or significant, caused no adverse effect since there were no deaths in eight patients.

The causes of death are shown in Table IV. Embolic accidents, pulmonary

TABLE IV. CAUSES OF DEATH AND TIME OF DEATH

CAUSE OF DEATH	GROUP 1	GROUP 2	GROUP 3	TOTALS	TIME OF DEATH
Hemorrhage	—	4	2	6	1-24 hr.
Ventricular fibrillation	—	1	3	4	Immediate
Pulmonary embolus	—	—	4	4	1-5 days
Cerebral embolus	—	1	2	3	5-10 days
Heart failure	—	1	1	2	5-28 days
Renal failure	—	1	—	1	3 days
Totals	—	8	12	20	

and cerebral, were responsible for more than one-third of the deaths. Hemorrhage and ventricular fibrillation were the next most frequent factors.

Correlation of mortality with clinical data found to be helpful in evaluating patients for mitral or aortic commissurotomy alone indicates that the anatomic diagnosis was the only significant prognostic factor, although there was a gross correlation between functional classification and survival (Table V).

TABLE V. PROGNOSTIC FACTORS IN MULTIVALVULAR SURGERY

	GROUP 1			GROUP 2			GROUP 3			TOTALS		
	NO.	DEATHS	(%)	NO.	DEATHS	(%)	NO.	DEATHS	(%)	NO.	DEATHS	(%)
1. Age												
20–30	1	—	—	3	—	—	3	3	100	7	3	42
30–40	4	—	—	20	6	30	8	1	16.5	32	7	22
40–50	6	—	—	15	2	13	9	6	67	30	8	27
50–60	—	—	—	1	—	—	4	2	50	5	2	40
2. Sex												
Male	2	—	—	14	3	21	13	6	46	29	9	31
Female	9	—	—	25	5	20	11	6	54	45	11	25
3. Heart Size												
Normal	4	—	—	3	1	33	—	—	—	7	1	14
1-plus	2	—	—	3	—	—	2	—	—	7	—	—
2-plus	5	—	—	15	4	27	12	6	50	32	10	31
3-plus	—	—	—	18	3	17	9	5	55	27	8	29
4-plus	—	—	—	—	—	—	1	1	100	1	1	100
4. Functional												
Class II	5	—	—	3	1	33	1	—	—	9	1	11
III	6	—	—	28	4	14	15	6	40	49	10	20
IV	—	—	—	8	3	38	8	6	75	16	9	56
5. Failure on admission												
Present	5	—	—	21	3	14	9	6	67	35	9	26
Absent	6	—	—	18	5	28	15	6	10	39	11	28
6. Angina												
Present	1	—	—	11	2	18	6	3	50	18	5	28
Absent	10	—	—	28	6	21	18	9	50	56	15	25
7. Left ventricular size												
Normal	8	—	—	9	2	22	7	3	43	24	5	21
1-plus	1	—	—	9	1	11	3	1	33	13	2	15
2-plus	2	—	—	15	4	26	11	6	54	28	10	36
3-plus	—	—	—	5	1	20	3	2	67	8	3	37.5
4-plus	—	—	—	1	—	—	—	—	—	1	—	—

Postoperative Hospital Course.—Cardiac complications without mortality occurred in twenty-three (42 per cent) of the surviving patients (Table VI). The most frequent complications were congestive heart failure, which occurred in eleven (20 per cent), and the development of atrial fibrillation which occurred in nine (33 per cent) of the twenty-seven patients with normal sinus rhythm.

Eight who developed failure were in Groups 2 and 3. Cardiac rhythm reverted to a normal sinus mechanism in six of the nine patients who had developed atrial fibrillation.

TABLE VI. POSTOPERATIVE COMPLICATIONS IN THE HOSPITAL

TYPE	GROUP 1	GROUP 2	GROUP 3	TOTALS
1. Cardiac				
Congestive failure	3	4	4	11
Pericarditis	1	—	—	1
Atrial fibrillation (converted)	1	4	1	6
Atrial fibrillation (not converted)	1	2	—	3
Paroxysmal tachycardia	—	1	1	2
Totals	6	11	6	23
2. Pulmonary				
Left effusion	6	15	9	30
Retained secretions (requiring bronchoscopy)	—	4	1	5
Totals	6	19	10	35
3. Miscellaneous				
Fever (unexplained)	1	7	1	9
Psychotic episodes	1	3	—	4
Anemia	—	3	1	4
Uremia	—	2	—	2
Drug reaction	—	1	—	1
Jaundice	—	1	—	1
Totals	2	17	2	21

Pulmonary complications without death were encountered in thirty-five (64 per cent) patients (Table VI). The presence of a left pleural effusion was considered a complication. Retained secretions requiring bronchoscopy occurred in five patients.

Of the miscellaneous complications, the presence of an unexplained febrile reaction which persisted longer than the fifth postoperative day was the most frequent and occurred in nine (16 per cent) patients. Other complications included jaundice, anemia, mental disturbances, impaired renal function, and drug reactions.

Follow-Up Review.—The postoperative evaluation (Fig. 1) was limited to those who had been operated on at least three months previously. Of the fifty-four patients surviving surgery, four died following discharge from the hospital (Table VII). Three of these deaths resulted from congestive heart failure four to five months after surgery, and one occurred in five months following subacute bacterial endocarditis. This represented a 7 per cent mortality in patients who were discharged from the hospital. The group classification and the time in months between surgery and the follow-up review of the remaining forty-one patients is indicated in Table VIII.

Fig. 1.—Comparison of pre- and postoperative symptoms.

TABLE VII. OVER-ALL FOLLOW-UP FIGURES

	GROUP 1	GROUP 2	GROUP 3	TOTALS
Total patients surviving operation	11	31	12	54
Deaths since operation	—	1	3	3
Observed less than 3 mo.	1	7	1	9
Follow-up over 3 mo.	10	23	8	41

TABLE VIII. LENGTH OF FOLLOW-UP PERIOD (41 PATIENTS)

	GROUP 1	GROUP 2	GROUP 3	TOTALS
(Months)				
3–6	3	10	1	14
6–12	2	5	6	13
12–18	4	7	1	12
18–24	1	1	—	2

Improvement was noted in thirty-four patients (83 per cent). The clinical status was unchanged in four (9 per cent), and three (7 per cent) were definitely worse. The outstanding changes observed were a decrease in fatigability and dyspnea. Three patients were entirely free of their former symptoms and are now leading normal lives without functional incapacity.

Less than one-half of the patients who experienced peripheral edema preoperatively were significantly improved. In nine (37 per cent) this complaint became more severe.

Five of the forty-one patients had angina preoperatively. The complaint disappeared in two patients and was not as severe in two others.

None who complained of syncope experienced an attack after surgery. Hemoptysis recurred in two of the eleven (18 per cent) who had reported this symptom preoperatively.

The three patients, who were considered worse after surgery, consisted of one with advanced tricuspid insufficiency, one with severe hypertension, and a third patient who was classified in this group because of severe and persistent incisional pain which interfered with all normal activity.

Ten patients had febrile reactions; in seven of these the temperature elevation was recurrent. In one patient jaundice finally developed and a diagnosis of hepatitis was established. In still another a persistent septic febrile reaction associated with splenomegaly, and microscopic hematuria which responded to massive doses of antibiotics established a clinical diagnosis of subacute bacterial endocarditis although a positive blood culture was not obtained. The antistreptolysin titer was elevated to 356 units in the third patient, suggesting an antecedent streptococcal infection if not an actual rheumatic reactivity. In the remaining seven patients the etiology of the temperature elevations remained obscure.

Insomnia, incisional pain, and mental disturbances were the additional symptoms which developed after discharge from the hospital.

No embolic accidents occurred in the late convalescent period. In three patients atrial fibrillation reverted to normal sinus rhythm, and in the same number atrial fibrillation replaced a normal sinus mechanism. Auscultatory changes noted in the follow-up period are listed in Table IX. The intensity of the aortic systolic murmur was decreased in eighteen patients (43 per cent), but in all instances the murmur retained its characteristic rough quality. A more significant change was noted in the intensity of the aortic second sound.

Of the thirty-five patients in the postoperative group in whom this sound had been diminished or absent, an increase in intensity was observed in twenty-nine (82 per cent). An early blowing diastolic murmur originating in the aortic area was heard in seven of the fourteen patients (50 per cent) in whom it was not present previously. However, this murmur did not indicate a dynamic aortic insufficiency. A mitral systolic murmur was heard in twelve of the twenty-one patients (57 per cent) in whom it was not heard preoperatively. Changes in the intensity of the mitral diastolic murmur were noted in thirteen of forty-one patients (31 per cent). These were not considered major alterations. The murmur actually disappeared in four patients (9 per cent). The duration and pitch of the mitral first sound were significantly altered in twenty-six (63 per cent).

TABLE IX. AUSCULTATORY CHANGES OBSERVED DURING FOLLOW-UP PERIOD

	NO.	(%)
Decrease in intensity of aortic systolic murmur	18	43
Increase in intensity of aortic second sound	29	82
Aortic diastolic murmur present now, absent preoperatively	7	50
Decrease in intensity of mitral diastolic murmur	13	31
Mitral diastolic murmur disappeared	4	9
Mitral systolic murmur present now, absent preoperatively	12	57
Change in duration and pitch of mitral first sound	26	63

Any alteration in the transverse measurement of the heart of 1 cm. or more was considered significant. In the six patients with normal heart size preoperatively no change in size was observed. Of the thirty-five patients with a cardiac enlargement of Grade 1 or greater, eighteen (51 per cent) remained unchanged. In twelve (29 per cent) the heart size decreased significantly, the greatest change measuring 3 cm. Five patients (14 per cent) had a significant increase in heart size ranging from 1 to 2 cm. A decrease in the size of the pulmonary artery appendageal segment was not considered significant since this resulted from amputation of the atrial appendage during surgery.

Aside from alteration in rhythm the most significant change noted in the electrocardiographic pattern was related to the findings of left ventricular hypertrophy and "strain." The T wave and RS-T segment changes characterizing this diagnosis became less marked in three of ten (30 per cent) patients, and these alterations could not be attributed to the withdrawal of digitalis. No change was noted in the nine patients with right ventricular hypertrophy patterns.

In all the patients in whom comparisons could be obtained the anacrotic notch on the brachial artery tracing disappeared, or a change in its abnormal position was noted following the Valsalva maneuver.

DISCUSSION

Although mitral and aortic stenosis were significant lesions, no conclusions were drawn as to which had the predominant effect on the physiology of the circulation. Criteria are lacking to permit this differentiation accurately and consistently. If, for example, the left atrium, and right and left ventricles are equally enlarged, does an electrocardiographic pattern of ventricular hypertrophy indicate which lesion is predominant? When all other manifestations are equal, can the major stenosis be decided by a comparison of the auscultatory findings? If so, is the quality or intensity of the murmurs and the more important feature to compare? Do right and left ventricular enlargements develop from identical degrees of mitral and aortic obstruction, or does one of these lesions have a more marked effect upon the size and hypertrophy of a ventricular chamber? Information related to the final answer to these questions can be obtained from an examination of both valves at the time of surgery, but this is technically difficult if not imprudent in combined commissurotomy. Furthermore, the valve size at operation does not necessarily indicate the degree of abnormal physiology which must follow.

A study of the symptomatology may serve as an additional guide. The subjective pattern in combined stenosis is made up of the symptoms which characterize the individual lesions. Where the manifestations of a particular involvement are more common it most likely follows that this lesion is predominant. Easy fatigability and dyspnea are not useful in this differentiation, since they are consistent, chronic complaints in both mitral and aortic disease. Hemoptysis and peripheral edema, however, are encountered earlier and more frequently in mitral disease. Angina and syncope reflect aortic valve involvement, since there is little reason to believe these symptoms arise from alterations in coronary and cerebral circulation as the result of mitral stenosis. With hemoptysis and edema the more usual complaints in this group of patients, and angina and syncope less frequent than in uncomplicated aortic disease, it may be argued correctly that mitral stenosis was the predominant lesion in the majority of instances. Furthermore, when cardiac enlargement was present the left atrium and right ventricle were involved three times as often as the left ventricle. Regardless of these facts and their implication, it remained true that both the mitral and aortic stenosis had a significant and separate influence upon the physiology of the circulation. Surgical treatment designed to correct one and not the other would have been poorly conceived and incomplete in its purpose.

The combination of mitral and aortic stenosis did not seriously obscure the auscultatory diagnosis of either abnormality. However, the likelihood of hearing a normal aortic second sound was twice as great as in uncomplicated aortic stenosis. This may have resulted from the transmission of an accentuated pulmonic second sound to the right of the sternum where it overshadowed the aortic sound.

The fact that the left ventricle usually was not enlarged in combined and uncomplicated stenosis suggests that the mitral valve obstruction effectively

spares this chamber unless mitral or aortic insufficiency exerts a dynamic opposing influence.

The average length of continuous medical treatment was 6.9 years, a considerably longer experience than that reported by patients with mitral or aortic disease alone. Digitalis or an allied product had been prescribed for an average of 4.6 years, and over one-half of the patients had received mercurial diuretics regularly for at least a year. The chronicity and severity of multivalvular disease exceeded that observed in isolated lesions and established a firm pattern from which postoperative comparisons could be drawn. From a subjective standpoint the relief in fatigability, dyspnea, hemoptysis, angina, and syncope was comparable to that seen in the surgical treatment of mitral or aortic stenosis alone. The failure of peripheral edema to respond suggested that the possibility of alleviating congestive heart failure in pure or complicated combined stenosis was much more limited than when the lesions occurred separately. Otherwise stated, combined commissurotomy is more effective in relieving other manifestations such as dyspnea, angina, syncope, or hemoptysis.

As in commissurotomy for single lesions, the most significant auscultatory changes after surgery were observed in the intensity and quality of the first mitral and second aortic sounds. For the present these objective changes may be regarded as important gains. It remained clear, however, that although changes in intensity were common, the characteristic murmur of aortic stenosis never disappeared and that of mitral stenosis rarely did.

The creation of a dynamic regurgitation in either valve is a major complication counter-balancing any benefit to be derived from surgery. Murmurs indicating some degree of regurgitation are commonly produced, but these are usually unaccompanied by the findings of physiologically significant defects and simply reflect the inability of modern surgical techniques to re-establish valve function according to its exquisitely exact and normal pattern.

In view of the major physiologic changes that must take place before a decrease in the transverse diameter of the heart is realized, this accomplishment must be regarded as an impressive gain, and an effective illustration of the potential worth of combined commissurotomy. Conversely, an increase in heart size can result from the production of a significant regurgitation, or the continuing effect of uncorrected complicating lesions. Failure to alter the size of the heart could not be correlated with the rate or degree of subjective improvement. This is consistent with the findings in commissurotomy for single lesions, and again stresses the need for precise information as to the correlation of symptoms, abnormal physiology, and anatomic changes.

No satisfactory evidence was uncovered in this study justifying the concept that rheumatic reactivity is common following valve surgery. If local trauma to endocardial tissue serves as the stimulus for reactivity it follows that combined commissurotomy increases that likelihood. However, episodic febrile reactions in convalescence were no more common in this group of patients than in those with either mitral or aortic surgery alone. The febrile illness which occurred most commonly in convalescence was characterized by a short clinical course, pain on deep inspiration transmitted to the left shoulder and neck along the

course of the phrenic nerve, and the physical findings of a pleuritis or pleuropericarditis. In only one of four cases studied was the antistreptolysin titer elevated. None of these patients developed the joint involvement of classic rheumatic fever. Until the exact etiology of this syndrome is determined it appears more reasonable to ascribe it to a traumatic pleuropericarditis with incomplete absorption of effusion than to rheumatic activity.

There was no mortality in combined commissurotomy for uncomplicated mitral and aortic stenosis. It would be foolhardy to expect this record to stand as the number of patients increases, but the results promise an exceptionally low mortality for this anatomic combination. The presence of an additional insignificant lesion raises the mortality rate just beyond that of aortic commissurotomy for pure stenosis and to over twice that of mitral commissurotomy. Two insignificant lesions increase the mortality to almost twice that of aortic commissurotomy and over four times that of mitral commissurotomy. When one or more additional major defects are present, one of every two patients fails to survive. The combination of anatomic lesions and their physiologic significance is the most important factor related to survival in combined commissurotomy.

When the dual operation is carried out before the age of fifty, the mortality for all groups is 27 per cent. This is three times the risk of aortic or mitral commissurotomy alone in that same age category.

On the basis of the experiences in this group of patients the indications for combined commissurotomy may be clarified. The primary indication is the presence of mitral and aortic stenosis which results in significant and progressive abnormal physiology. Any combination of the clinical manifestations of this fact is acceptable indication provided none of the contraindications are present.

Additional significant lesions with the possible exception of mitral insufficiency and the presence of congestive heart failure are firm contraindications. Insignificant lesions, an age beyond fifty, and a functional class of three or greater add to the operative risk but are not contraindications. A systolic pressure which is persistently below 100 mm. Hg is a poor prognostic sign because of an implied decrease in renal flow and filtration following operation and serves as a deterrent below the age of fifty and a contraindication thereafter. As in surgery for other types of rheumatic heart disease, acute rheumatic activity, subacute bacterial endocarditis, and associated major disease are contraindications.

CONCLUSION

Except for those with the infrequent combination of uncomplicated mitral and aortic stenosis, patients with multivalvular disease are poorer operative risks than those with isolated lesions and offer less promise in functional recovery particularly when congestive failure has once occurred. At the same time surgery has accomplished subjective and objective improvement otherwise impossible even under prolonged and carefully regulated medical routines. The calculated risk in survival and the gravity of the postoperative complications emphasize a sober approach to the problem of multivalvular surgery and emphasize the need for careful patient selection.

SUMMARY

1. An evaluation of the surgical management of combined mitral and aortic stenosis is described in which the mortality and complications are analyzed and the preoperative clinical and objective findings in seventy-four patients are compared with those found three to twenty-four months after operation.

2. The operative mortality has been correlated with the presence of additional valvular lesions, the age of the patient, the functional status, the size of the heart, and the presence of angina.

3. Comparisons are drawn between the operative mortality for mitral and aortic commissurotomy alone and that of combined commissurotomy.

4. A significant improvement is noted in the symptoms of fatigability, dyspnea, and angina. However, improvement in peripheral edema was limited.

5. The improvement noted in heart size, brachial artery tracings, and electrocardiographic patterns was more limited than the alterations in the symptomatology and could not be correlated with them or with one another.

6. The indications and contraindications for combined commissurotomy are outlined.

SUMMARIO IN INTERLINGUA

1. Es presentate un evalutation del curso chirurgic de 74 patientes de combinate stenosis mitral e aortic.

2. Le mortalitate operative es studiate in su correlation con le presentia de altere lesiones valvular, le etate del patiente, su stato functional, le dimensiones del corde, e le presentia de angina de pectore.

3. Es comparate le mortalitate operative in commissurotomia o mitral o aortic con le mortalitate in casos de commissurotomia combinate.

4. Es comparate le constatationes clinic e objective ante e 3 a 24 menses post le operation. Un melioration significative es notate in le symptomas de fatigabilitate, dyspnea, e angina. Le melioration de edema peripheric esseva limitate. Le melioration in dimensiones cardiac, arteria brachial, traciamentos, e configurationes electrocardiographic esseva plus limitate que le alterationes symptomatologic. Le factores del prime de iste duo categorias monstrava nulle correlation o inter se o con alterationes symptomatologic.

5. Le autores discute indicationes e contraindicationes pro combinate commissurotomia.

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ORAL MERCURIAL DIURETICS: MERCUMATILIN IN THE TREATMENT OF CONGESTIVE HEART FAILURE

SIM P. DIMITROFF, M.D., RAND C. LEWIS, M.D., M. C. THORNER, M.D., AND JOHN B. FIELD, M.D., PH.D.

LOS ANGELES, CALIF.

THE high incidence of toxicity and of intolerance to oral mercurial diuretics has been a great deterrent to wide usage. Instances of untoward effects have been reported in from 33 per cent to 50 per cent of patients taking oral mercurial diuretics.[1-3] The efficacy of an oral preparation is a direct function of the amount of mercury absorbed. In clinical practice, however, the desired effect of increased efficiency with larger doses has been limited by the rising probability of intolerance. For some time, this laboratory has been evaluating oral mercurial diuretics, in part, with the object of finding means to reduce the patient load of the cardiac clinic, and with the hope of developing a more efficient therapeutic regimen that would lead to a decrease in the frequency of costly visits by nurses who give mercurial injections at the homes of patients physically unable to attend the clinic.

The first essential toward the realization of this program was to achieve a satisfactory diuretic effect maintaining the patient at or near his edema-free or basal weight. At the same time, it was important to avoid the secondary effects of a salt loss which may accompany repeated parenteral injections of mercurials. But diuretic effectiveness alone was not the only criteria. It became necessary to note that the oral diuretic did not produce an undue amount of gastrointestinal intolerance such as vomiting, nausea, diarrhea, intestinal colic; renal albuminuria or hematuria; skin reactions or stomatitis; or reactions secondary to electrolyte depletion. A previous paper from this laboratory related observations in an attempt to devise a satisfactory oral regimen with a new mercurial drug. In the present report, a new oral diuretic, mercumatilin,* (Cumertilin) was evaluated both for its diuretic properties in outpatients with congestive heart failure, and for the incidence and nature of toxic reactions.

While this study was in progress, Pollock and Pruitt[4] reported that oral mercumatilin can be given to patients with congestive heart failure for prolonged

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From the Department of Medicine (Cardiology), University of Southern California, School of Medicine, and the Los Angeles County Hospital, Los Angeles, Calif.

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*Cumertilin is the trade name of mercumatilin. Each tablet contains the equivalent of 20 mg. each of mercury and theophylline. The drug was supplied by Dr. Samuel M. Gordon of Endo Products Inc., Richmond Hill, N. Y.

TABLE I. SUMMARY OF LONG-TERM TREATMENT WITH ORAL MERCUMATILIN

	PATIENT	CARDIAC DIAGNOSIS*	CLASSIFICATION (CLASS 3)	DAILY TABLET DOSE	DURATION THERAPY (MO.)	TOTAL NO. TABLETS	DIURETIC RESULT	TOXICITY
1.	G.H.	H/ASHD	C	2 3× weekly	2	48	Good	None
2.	W.M.	H/LHD	C	2	2 intermittent	112	Good	None
3.	M.H.	HHD	C	3 3× weekly	1	36	Good	None
4.	B.B.	H/HD	C	alternating 1 and 2	12	520	Good	None
5.	E.B.	RHD	C	3 3× weekly	9	351	Good	None
6.	E.L.	LHD	C	1 4 days/wk.	4½	70	Good	None
7.	M.K.	ASHD	C	3	1	84	Good	None
8.	C.R.	H/HD	D	2	2	112	Poor	None
9.	E.S.	H/LHD	D	3 2× weekly	2	48	Good	None
10.	M.Z.	RHD	C	2 then 3	2	144	Good	None
11.	B.M.	HHD	C	3 on alternate days	4	153	Good	None
12.	J.P.	ASHD	C	3 3× weekly	2	72	Good	None

13.	E.S.	HHD	C	3 2× weekly	1	24	Good	None
14.	C.R.	H/ASHD	D	3 3× weekly	3	117	Good	None
15.	M.M.	H/ASHD	C	3 3× weekly	1	36	Good	None
16.	J.H.	RHD	D	3 on alternate days	2½	90	Good	None
17.	M.A.	RHD	D	2 then 3	1	72	Good	None
18.	F.L.	RHD	C	3	3/4	63	Poor	Cramps, diarrhea (antecedent gastritis)
19.	B.V.	ASHD	C	2	2/4	28	Poor	None
20.	V.M.	RHD	C	2	9	182	Good	None
21.	E.H.	ASHD	C	3	8	700	Good	None
22.	D.D.	ASHD	C	3 3× weekly	7	210	Good	None
23.	F.F.	H/ASHD	C	3 3× weekly	7	200	Good	None
24.	T.S.	ASHD	C	3 2× weekly	7	200	Good	None
25.	A.B.	ASHD	C	3 3× weekly	3	90	Good	None

*ASHD=Arteriosclerotic heart disease; HHD=Hypertensive heart disease; RHD=Rheumatic heart disease; LHD=Luetic heart disease.

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periods without notable appearance of toxic manifestations. They reported also that twenty of their twenty-five patients could be maintained on the tablets without need for parenteral therapy.

METHOD OF STUDY

Patients studied were those with chronic congestive heart failure attending the outpatient Cardiac Clinic of the Los Angeles County Hospital as well as a small number of patients seen in private practice. Clinically all had demonstrated a need for continuing mercurial diuretic therapy and had previously been on either repetitive doses of parenteral mercurial diuretics, or another form of oral mercurial preparation.

The criteria used in evaluating a satisfactory therapeutic response to the drug were a reduced need for frequent parenteral mercurial injections and the maintenance of basal weight as well as the absence or minimal presence of peripheral edema, pulmonary râles, or hepatomegaly.

Twenty-five patients cooperated adequately for a period of 1 to 12 months. Most were in the age group 50 to 70 years. There were fourteen females and eleven males. Sixteen had hypertension with or without arteriosclerotic heart disease, three had luetic heart disease, and six had rheumatic heart disease. All were in functional therapeutic Class 3C, except five who were in Class 3D. Initially all were observed at weekly intervals. It became apparent later that visits once every 2 to 3 weeks were sufficient, the periods between observations being extended on the basis of improvement in the patient's condition.

RESULTS

Twenty-two of the twenty-five patients were able either to maintain their edema-free weight, or lose even more fluid than could be accounted for by injection-induced diuresis. They did not show an increase in liver size, nor were pulmonary râles present. The patients felt less dyspneic, more comfortable, and demonstrated no evidence of salt depletion. They were able to continue with their limited activities with less distress and in some instances even to increase them without discomfort. They were permitted to increase their daily salt intake by use of table salt when it became apparent that mercumatilin tablets maintained basal weight even when a more liberalized salt intake was allowed. Table I shows the summary of findings in this group. It will be seen that the dosage of the drug was extremely variable, being graded in accordance with the response of each patient. This is understandable since the treatment of patients in congestive failure must be highly individual.

Most patients required three tablets daily, two or three times per week, or about one tablet daily as an average. One patient tolerated alternate doses of one and two tablets daily for one year.

Three patients failed to improve with the oral medications, as shown in Table I.

Patient F.L. was a postmitral commissurotomy patient, whose congestive failure increased in spite of cardiac surgery and all conventional medication. She complained of cramps, nausea, and diarrhea. However, she had an antecedent gastritis, which may have been a contributory factor in her intolerance. She had hepatomegaly which was difficult to reduce with parenteral mercurials. One mercumatilin tablet was given three times daily for three weeks in an attempt to reach a high, continuous level of mercurials, and to obtain diuresis. This endeavor failed, possibly because of inability to achieve adequate dosage. Under the conditions of this clinical trial it did not appear that the patient could be expected to respond to an oral diuretic, especially in view of her poor response to injected mercurials.

The second failure, B.V., had coronary artery disease and was in gradual progressive failure. There were wide weight fluctuations, even while she received weekly mercurial injections during the preceding two years. Because of the sudden unpredictable changes in her water retention, it was decided that an attempt to obtain a more "constant intra-tissue mercury" level might prevent the wide swings in her congestive state. As in patient F.L., however, this failed, and the patient showed increased fluid retention while on one tablet, twice every day.

The third patient, C.R., a 51-year-old hypertensive individual, was considered to be a failure, even though he had responded satisfactorily to one tablet, twice daily for two weeks. Taking advantage of his improved state, he began to salt his food heavily which resulted in progressive congestive failure for which he was hospitalized.

The necessity for the simultaneous use of oral and parenteral diuretics was observed in one patient who could not remain edema-free on oral preparations alone. Patient V.M. was 54 years old, with rheumatic heart disease of a duration of 20 years. Prior to oral mercurial diuretics she had to receive semiweekly or weekly mercurial injections, to control her weight and prevent symptoms of congestive failure. She received mercumatilin, one tablet twice daily, and was able to prevent edema and the recurrence of symptoms and signs of failure. Thus stabilized, she required parenteral mercury only once or twice a month, whereas prior to oral therapy six to eight injections were required per month. She was on this combined therapy for nine months with no untoward results and with the maintenance of a symptom-free state.

Except for the gastrointestinal symptoms reported by F.L., who was already known to have gastritis, there was no instance of toxicity or intolerance in any of the patients. Also, unlike the experience with another oral mercurial diuretic[5] there was no evidence of abnormalities in the urine such as albuminuria or changes in the blood chemistry as azotemia in several patients who had been receiving mercumatilin over a period of several months.

DISCUSSION

Oral mercumatilin is a diuretic which would appear to have an established place in the therapy of congestive heart failure. It follows the pattern of many other mercurial diuretics insofar as they alone are not adequate in the management of severe, acute, or rapidly progressive cardiac decompensation. The parenteral diuretics still remain the drug of choice in these situations, but the adjunctive use of mercumatilin tablets appears to offer a satisfactory therapeutic schedule.

The advantageous role played by mercumatilin tablets is in the management of the patient with congestive cardiac failure who has been brought to or near basal weight with parenteral mercurials. The oral diuretic then assists in the maintenance of this optimal weight by promoting the continuance of diuresis thus tending to keep the patient symptom-free. It may also permit a more palatable diet with liberalized salt intake.

Aside from gastrointestinal symptoms in one patient, to which mercumatilin questionably contributed, no evidence of toxicity or intolerance was encountered. This is a distinct advance in oral diuretics, all the more emphasized by the favorable response of twenty-two of the twenty-five patients observed. The high degree of tolerance to the drug by patients in the 50 to 70 year age groups, which comprised the greatest number of patients observed, indicates its safety.

It is of interest that most patients had hypertension or arteriosclerosis as the etiology of their cardiac failure. These are the causative categories which as a rule may be considered as progressively deteriorating, and it is in this particular group that oral mercumatilin was able to obviate the need of mercurial diuretic injections.

The use of oral mercurial diuretics to prolong the time interval when such injections would be necessary is a desirable and practical procedure, which has both primary and secondary advantages. The first is maintaining the patient symptom-free for longer periods with none or fewer injections, and the second is reducing the patient load in a cardiac clinic and the frequency of visits by home care physicians and nurses. It was found that as the "chronic clinic patients" could be satisfactorily maintained, the clinic physicians were enabled to spend more time with individual patients.

SUMMARY

Oral mercumatilin (Cumertilin) satisfactorily controlled congestive heart failure in twenty-two of twenty-five patients without evidence of intolerance or toxicity. Three patients exhibiting unstable or rapidly progressive congestive failure were not benefited.

SUMMARIO IN INTERLINGUA

Mercumatilina (Cumertilina) in administration oral resultava in 22 inter 25 patientes in un controlo satisfacente de congestive insufficientia cardiac. Illo non produceva ulle symptoma de intolerantia o toxicitate. Tres patientes, qui exhibiva congestive insufficientia cardiac in formas instabile o rapidemente progredente, non beneficiava del tractamento. Nos habeva le impression que le effecto de mercumatilina esseva specialmente benefic in le tractamento ulterior de patientes de insufficientia cardiac qui jam habeva attingite un peso approximativemente basal sub le influentia de un mercurial in administrationes parenteral.

Tablettas de mercumatilina representa pro le patiente un importante avantage therapeutic in tanto que illos reduce su requirimento de frequente injectiones de un mercurial e consequentemente le necessitate de su visitas septimanal al clinica. Isto allevia etiam le carga de labor del clinica e abassa le costo del therapia diuretic.

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FURTHER OBSERVATIONS OF CARDIOVASCULAR EFFECTS OF PENTAERYTHRITOL TETRANITRATE IN ANIMALS AND MAN

TRAVIS WINSOR, M.D., AND CHARLES C. SCOTT, PH.D., M.D.

LOS ANGELES, CALIF.

PREVIOUS studies on pentaerythritol tetranitrate for the prophylaxis of angina pectoris have shown that the oral administration of this agent increases exercise tolerance, decreases nitroglycerin requirement, and has a normalizing effect on the negative S-T segment shifts which occur in patients with angina pectoris and coronary insufficiency.[1-3] The present study was carried out to determine if pentaerythritol tetranitrate (PETN) (1) dilates the coronary arteries in a manner similar to nitroglycerine,[4,5] (2) produces peripheral arterial vasodilatation, (3) is effective sublingually since this route might allow more rapid absorption, (4) is absorbed through the pulmonary route, and (5) compares favorably in effectiveness with other nitrates in the prophylaxis of angina pectoris.

METHODS AND MATERIALS

Animal studies included thirty-nine observations on twenty-one mongrel dogs weighing an average of 20 kilograms. The anesthetic employed was secobarbital sodium. Blood pressure was recorded from the femoral artery by means of a Statham strain gauge connected to a Sanborn direct-writing recorder. A rotameter was used to record coronary blood flow according to the technique of Shipley and Wilson.[6] Blood flow was recorded simultaneously with blood pressure. The operative technique for blood flow was a modification of that described by Windbury and associates.[7] Portions of the fourth and fifth ribs were removed from the left thoracic cage, which allowed adequate exposure of the heart and coronary arteries. The anterior descending branch of the left coronary artery was perfused with blood from the left carotid artery. Studies were made before and after the sublingual administration of hypodermic tablets of PETN* or nitroglycerin. The tablets were placed on the buccal mucosa and were moistened with a few drops of water to cause them to disintegrate rapidly.

From the Heart Research Foundation, Hospital of the Good Samaritan, Los Angeles, Calif.

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*Pentaerythritol tetranitrate was supplied as special sublingual Peritrate tablets by Dr. Walter H. Hoskins, Warner-Chilcott Laboratories, New York N. Y.

The pastelike mixture was rubbed into the mucosa with a glass stirring rod.

The human studies were carried out on eighty-three patients with coronary insufficiency and angina pectoris. The average age was 54 years; range, 38 to 76. The patients were white, ambulatory clinic patients with well established angina of at least three years' duration. A report card system was employed for recording the number of attacks of chest pain and the amount of nitroglycerin used. These cards were reviewed bimonthly. Skin temperatures were recorded with a four-point Thermistor Thermometer.[8] Plethysmograms were made with an electronic pneumoplethysmograph.[9] The collecting cuff was placed at the ankle or wrist. Exercise tests were carried out on a portable treadmill set at a 10° incline with the floor and which moved at a rate of one mile per hour. Ballistocardiograms were recorded using a low-frequency horizontal table with a natural frequency of 1.5 cycles per second with critical damping.[10] The recordings were made on a Sanborn Poly-Viso with simultaneous recording of other physiologic phenomena. All records were taken with the breath held at the peak of a normal inspiration.

TABLE I. COMPARISON OF THE CORONARY DILATING ACTIONS OF PETN AND NITROGLYCERIN ADMINISTERED SUBLINGUALLY TO DOGS

DRUG	DOSE	NO. OF TESTS	MAXIMUM CHANGE OF BLOOD PRESSURE (%) MEAN	S.E.	MAXIMUM CHANGE OF BLOOD FLOW (%) MEAN	S.E.	TIME TO MAXIMUM (MIN.)
	(milligram)						
PETN	10	3	0.0		+ 1.0		—
	20	2	−10.0		+25.0		17.0
	40	15	− 6.1	±4.6	+11.5	±9.4	18.3
	100	1	− 5.0		+11.0		26.0
	(grain)						
	1/100	2	− 5.0		− 4.0		3.0
Nitroglycerin	1/50	7	−31.9	±7.1	−11.1	±16.3	4.4
	1/25	9	−37.9	±5.2	−11.3	±17.0	3.2

RESULTS

The effects of sublingually administered PETN and nitroglycerin on the coronary blood flow and blood pressure are shown in Table I. The sublingual administration of 40 mg. of PETN resulted in an average increase in coronary flow of 11.5 per cent, which was associated with a blood pressure fall which averaged 6.1 per cent. This indicates coronary vasodilation (Fig. 1). Nitroglycerin 1/50 grain was followed by an average fall of 11.1 per cent in coronary flow and an average fall of 31.9 per cent in blood pressure. This also probably represents coronary vasodilation (Fig. 2). The average time of onset of action after PETN was 9 minutes after administration, and with nitroglycerin it was 1 minute after administration. The average time to reach maximum effect after 40 mg. of PETN was 18.3 minutes, and after 1/50 grain of nitroglycerin it was 4.4 minutes. The duration of the cardiovascular effects of PETN and

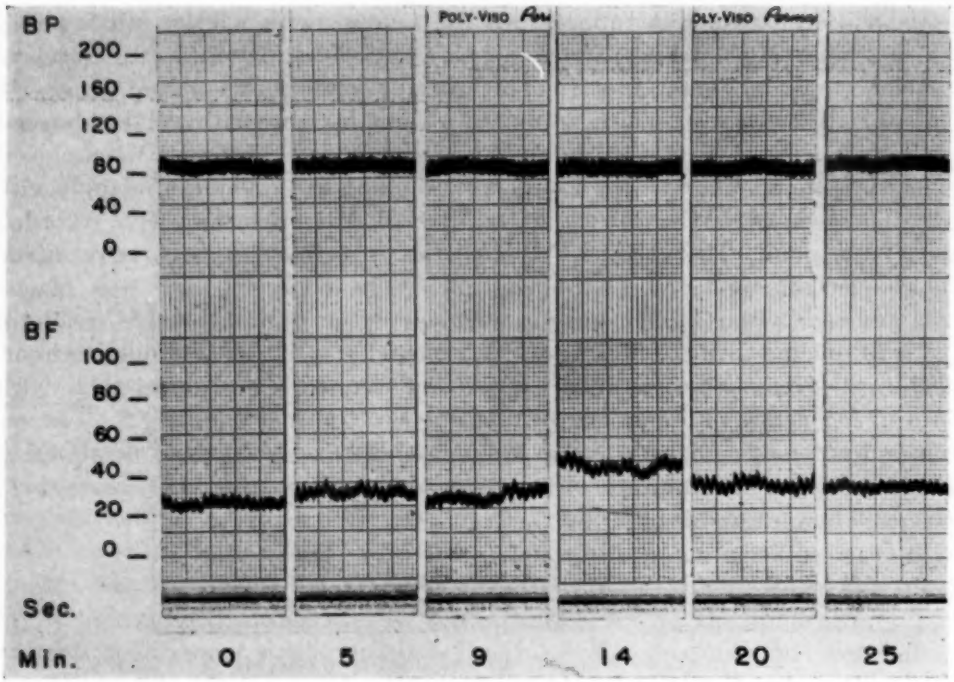

Fig. 1.—Effect of PETN on coronary blood flow of an anesthetized dog. Top line is blood pressure in millimeters of mercury. Bottom line is blood flow in the anterior descending branch of the left coronary artery and is measured in milliliters per minute. At zero minutes PETN 40 mg. was administered by sublingual route.

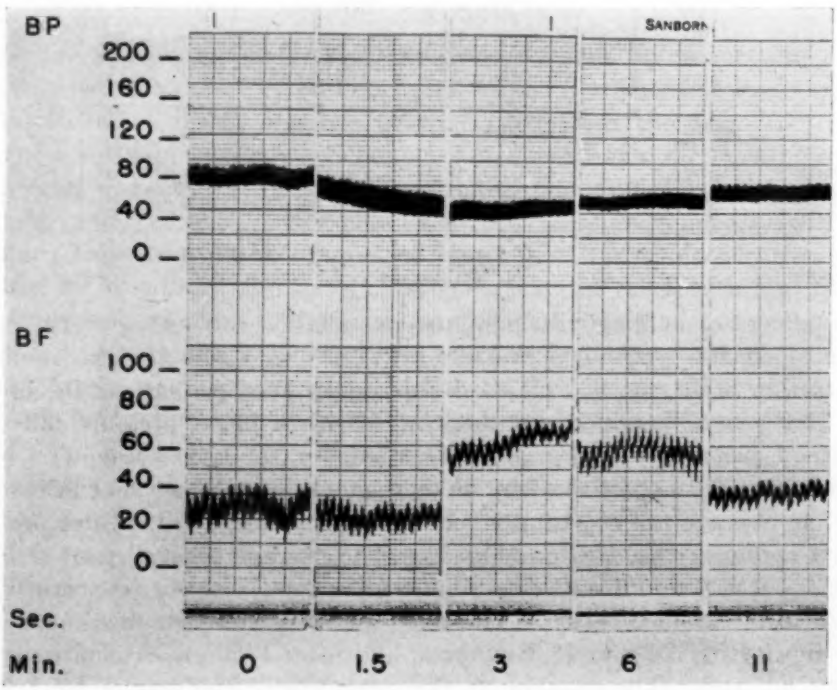

Fig. 2.—The effect of nitroglycerin on the coronary blood flow in an anesthetized dog. The top line is the blood pressure in millimeters of mercury. The bottom is the blood flow in the anterior descending branch of the left coronary artery and is measured in milliliters per minute. At zero minutes nitroglycerin 1/25 grain was administered by the sublingual route.

nitroglycerin could not be estimated with accuracy because of the effects of the anesthetic, the surgery, and of other factors which could not be controlled adequately during a long period of time.

The effect of PETN on the cardiovascular system of man was as follows: heart rate and blood pressure were studied in twelve subjects before and after 20 mg. sublingually (Table II). All patients were studied in the horizontal position, and records of pulse rate were recorded from the ballistocardiogram. Blood pressure was determined with the sphygmomanometer. The average pulse rate before the drug was 67 beats per minute. The highest pulse rate was reached 3 minutes after administration, the average being 70.7 beats per minute. The average blood pressure before the drug was 145/96 mm. Hg and 3 minutes after the drug the average was 144/94 mm. Hg.

TABLE II. THE EFFECT OF PETN ADMINISTERED SUBLINGUALLY ON HEART RATE

PATIENT NO.	HEART RATE (BEATS PER MINUTE)					
	BEFORE PETN	MINUTES AFTER PETN				
		1	2	3	4	5
1	47	54	54	50	50	49
2	60	60	60	60	60	60
3	60	68	68	64	63	63
4	71	74	83	84	80	78
5	70	74	74	74	72	72
6	80	82	81	80	80	80
7	80	89	87	87	86	86
8	63	64	64	65	65	64
9	62	62	62	62	62	62
10	71	71	74	79	79	70
11	70	70	70	70	70	70
12	70	70	70	73	75	74
Mean	67.0	69.8	70.6	70.7	70.1	69.0
Min.	47.0	54.0	54.0	50.0	50.0	49.0
Max.	80.0	89.0	87.0	87.0	86.0	86.0

Skin temperatures of forehead, finger, and toe of seven patients were studied before and after 20 mg. of PETN sublingually (Table III). The forehead temperature was 34.7° C. before and after the drug. The finger temperature changed on the average from 33.0 to 33.6° C., and the toe temperature changed on the average from 29.2 to 29.3° C.

The pulsations and relative blood flow to the toes before and after 20 mg. of PETN sublingually were studied in seven patients (Table IV). The average pulsation before the drug was 1.4 cubic millimeters, while after the drug the average was 2.6 cubic millimeters. Indirect body heating was then applied in a manner already described,[9] after which the pulsations increased to an average of 4.8 cubic millimeters. The average relative blood flow was 3.2 cubic millimeters per 4 c.c. of toe per second before the drug, while after, it was 5.0 as

compared with indirect body heating, which averaged 15.1. Examples of the slight peripheral vasodilation with sublingual PETN in a normal subject and a patient with moderate peripheral arteriosclerosis are shown in Figs. 3 and 4.

TABLE III. THE EFFECT OF PETN ADMINISTERED SUBLINGUALLY ON SKIN TEMPERATURES

PATIENT NO.	SKIN TAMPERATURE °C.					
	FOREHEAD		FINGER		TOE	
	BEFORE PETN	5 MIN. AFTER DRUG	BEFORE PETN	5 MIN. AFTER DRUG	BEFORE PETN	5 MIN. AFTER DRUG
13	34.4	34.4	33.0	33.5	28.0	28.0
14	35.0	35.0	32.0	32.2	30.0	30.2
15	34.8	34.9	34.0	34.5	29.1	29.1
16	34.5	34.4	32.2	32.8	28.2	28.3
17	35.1	35.1	32.0	32.8	30.0	30.0
18	35.0	35.0	34.1	34.6	28.2	28.3
19	34.3	34.4	34.0	35.0	31.0	31.1
Mean	34.7	34.7	33.0	33.6	29.2	29.3
Min.	34.3	34.4	32.0	32.2	28.0	28.0
Max.	35.1	35.1	34.1	35.0	31.0	31.1

TABLE IV. THE EFFECT OF PETN ADMINISTERED SUBLINGUALLY ON THE HEIGHT OF PULSATIONS AND RELATIVE BLOOD FLOW OF TOES

PATIENT NO.	TOE					
	PULSATIONS CU.MM.			RELATIVE FLOW CU.MM./4 C.C./SEC.		
	BEFORE PETN	AFTER DRUG	AFTER INDIRECT BODY HEAT	BEFORE PETN	AFTER DRUG	AFTER INDIRECT BODY HEAT
20	2.0	3.5	6.0	5.0	7.0	18.0
21	0.1	1.8	3.0	1.2	2.0	8.0
22	0.5	0.8	5.0	1.0	3.0	20.0
23	2.0	4.0	6.1	5.5	7.0	17.0
24*	0.5	1.5	3.2	3.0	4.5	10.0
25*	1.5	2.5	3.8	2.8	5.7	11.0
26	3.0	4.5	6.5	4.0	6.0	22.0
Mean	1.4	2.6	4.8	3.2	5.0	15.1
Min.	0.1	0.8	3.0	1.0	2.0	8.0
Max.	2.0	4.5	6.5	5.5	7.0	22.0

*Peripheral arteriosclerosis.

The force of the cardiac contraction was studied by measuring the amplitude of the I-J wave in twelve patients before and after an average of 22.5 mg. of PETN administered sublingually (Table V). Before the drug the average I-J wave measured 5.7 mm., while after an average of 4.4 minutes it reached its

peak amplitude, which averaged 6.8 mm. A control study was carried out in the same group of patients in which a record was taken before and after 4.4 minutes of rest. The average amplitude before was 5.6 mm. and after 5.7 mm.; thus it is felt that the increase after PETN, although slight, is significant. A typical record is seen in Fig. 5.

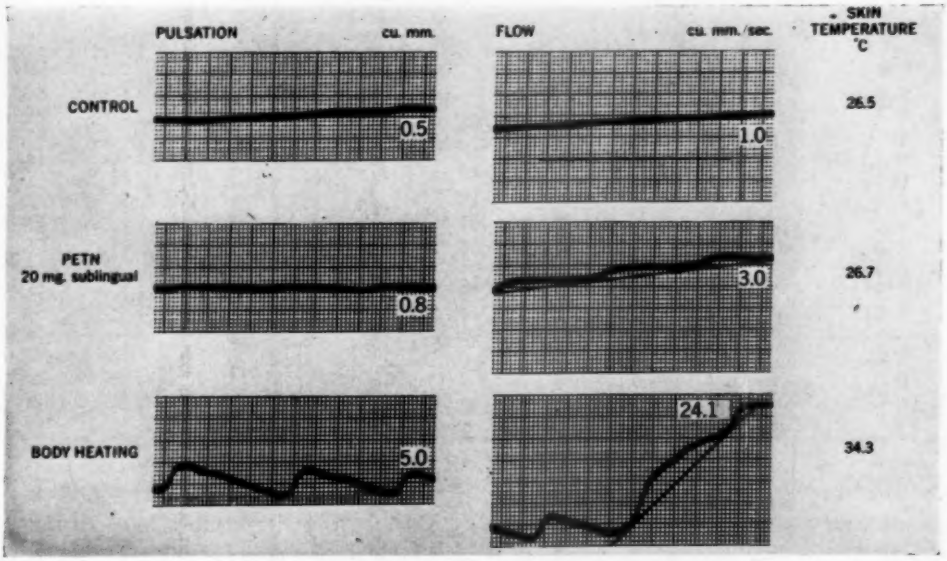

Fig. 3.—Pulsations, blood flow, and skin temperatures of the left second toe in a patient with angina pectoris without peripheral vascular disease. The measurements increased only slightly after 20 mg. of PETN sublingually, whereas body heating produced marked increases.

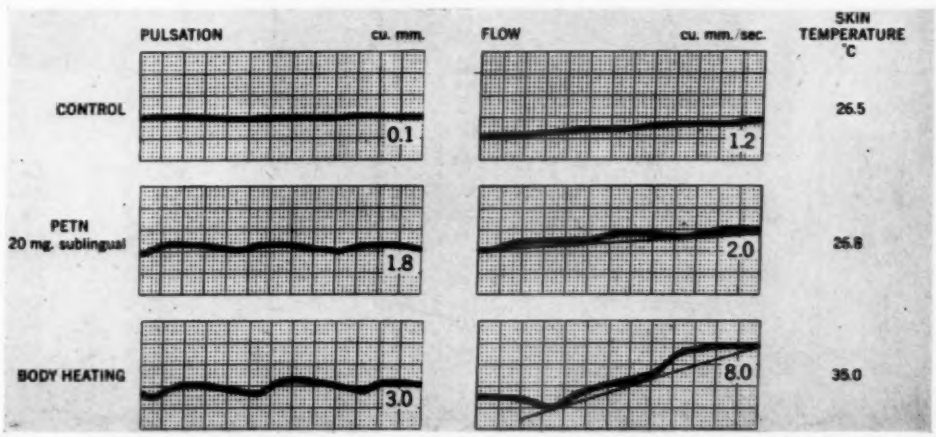

Fig. 4.—Pulsations, blood flow, and skin temperatures of the left second toe of a patient with angina pectoris who in addition has peripheral arteriosclerosis. The measurements increased only slightly after 20 mg. of PETN sublingually, whereas body heating produced larger changes.

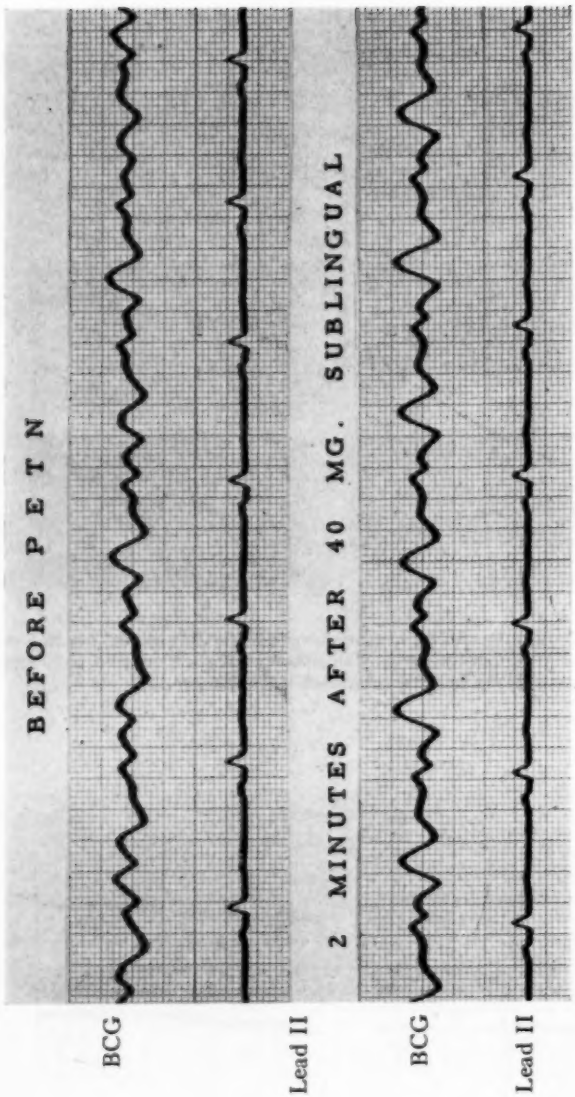

Fig. 5.—The ballistocardiogram shows an increase in the amplitude of the I-J wave after 40 mg. of PETN sublingually.

TABLE V. EFFECT OF PETN SUBLINGUALLY ON THE AMPLITUDE OF THE I-J WAVE OF THE BALLISTOCARDIOGRAM

PATIENT NO.	AMPLITUDE OF I-J WAVE IN BALLISTOCARDIOGRAM				
	BEFORE AND AFTER PETN			BEFORE AND AFTER REST	
	BEFORE	AFTER DRUG	MIN. AFTER DRUG	BEFORE	AFTER 4.4 MIN. REST
27	6.0	6.0	5	5.0	4.0
28	2.0	3.0	4	3.0	4.0
29	6.0	6.0	4	5.0	5.0
30	7.0	9.0	3	7.0	7.5
31	1.0	3.0	3	1.5	1.0
32	6.0	6.0	4	6.0	6.0
33	3.0	4.0	5	2.5	3.0
34	7.0	8.0	5	7.0	7.0
35	6.0	7.0	6	6.0	6.5
36	4.5	6.0	5	4.0	4.5
37	10.0	11.5	5	10.0	9.5
38	10.0	12.0	4	10.0	10.0
Mean	5.7	6.8	4.4	5.6	5.7
Min.	1.0	3.0	3.0	1.5	1.0
Max.	10.0	12.0	6.0	10.0	10.0

The effect of PETN on the time the patients could walk on a treadmill was studied in twelve patients (Table VI). The test was carried out on two successive days. Patients reported to the clinic in a fasting state, and after a 15-minute rest at a room temperature of 24 ± 1° C. they walked until first evidence of precordial pain developed. The time of the walk was recorded. PETN in an average dose of 25 mg. was given immediately sublingually, followed by a

TABLE VI. EFFECT OF PETN ADMINISTERED SUBLINGUALLY ON EXERCISE TOLERANCE

PATIENT NO.	SECONDS WALKED ON TREADMILL					
	NO DRUG	PETN	DIFF.	NO DRUG	PLACEBO	DIFF.
47	125	125	0	125	130	5
48	100	250	150	112	120	8
49	70	105	35	68	65	3
50	180	280	100	170	190	20
51	125	440	315	130	250	120
52	196	224	28	200	205	5
53	155	335	180	168	185	17
54	66	195	129	60	57	−3
55	150	365	215	160	252	92
56	100	300	200	108	242	134
57	135	350	215	130	142	12
58	80	115	35	98	84	−14
Mean	123.5	257.0	133.5	127.4	160.0	32.8
Min.	66	105.0	0	60.0	57.0	−14
Max.	196	440.0	315	200.0	252.0	134

3-minute rest period. The patients then repeated the walk and the time to produce chest pain was again noted. The following day each patient was retested using a placebo instead of PETN. The average walking time before PETN was 123.5 seconds and 257.0 seconds after the drug. That is, the patients walked an average of 133.5 seconds longer after taking PETN. Placebo tests averaged 127.4 seconds before, and 160.0 seconds after placebo, or an increase in walking time of 32.8 seconds. The improved walking time with PETN as compared with the placebo indicated that this drug increased exercise tolerance.

An attempt was made to treat acute attacks of angina pectoris with PETN in doses of 10 and 20 mg. sublingually (Table VII). Twenty patients were studied and the results were compared with nitroglycerin and placebos. The results show that nitroglycerin generally was more effective in relieving acute attacks than was PETN, owing evidently to the slower onset of action of the latter. The high rate of apparent relief with placebos is due probably to the short duration of the untreated attacks.

TABLE VII. RESULTS OF TREATMENT OF ACUTE ATTACKS OF ANGINA PECTORIS EMPLOYING NITROGLYCERIN AND PETN SUBLINGUALLY; NITROGLYCERIN ACTED EARLIER AND GAVE MORE COMPLETE RELIEF OF PAIN

PATIENT NO.	AMOUNT OF RELIEF OF ACUTE ATTACK OF ANGINA PECTORIS*			
	NITROGLYCERIN 1/150 GRAIN	PETN SUBLINGUAL		PLACEBO
		10 MG.	20 MG.	
1	+++	0	0	0
4	+++	0	0	0
3	+++	+	++	++
2	+++	+	++	+++
9	+++	0	+	0
19	+++	0	0	0
28	+++	0	0	0
17	+++	+	+	+++
14	+++	++	++	0
16	+++	++	++	++
32	+++	0	+	0
40	+++	+	+++	++
42	+++	+	++	+
47	+++	+++	+++	++
44	+++	++	+++	+++
46	++	++	+++	0
49	++	+	++	0
52	+++	++	++	++
54	+++	+++	+++	+++
55	++	+++	+++	+++

0 = no relief of angina
+ = partial relief in 6 min.
++ = complete relief in 6 minutes
+++ = complete relief in 3 minutes
*The first 5 subjects had relief of postprandial angina if 20 mg. was taken sublingually 20 minutes before eating.

The effect of the inhalation of PETN powder during the early acute stage of angina pectoris was studied in eight patients. Four patients were unable to

relieve acute attacks of angina with 6 mg.; however, four patients obtained relief when 19 mg. of the drug was inhaled. The relief occurred more slowly than that produced by sublingual nitroglycerin 1/150 grain, which was used as a control in all patients.

TABLE VIII. EFFECT OF LARGE AND SMALL DOSES OF PETN ADMINISTERED ORALLY ON NITROGLYCERIN REQUIREMENT; LARGE DOSES WERE MORE EFFECTIVE THAN SMALL DOSES

PATIENT NO.	CONTROL NO PETN	LARGE DOSE PETN		SMALL DOSE PETN	
	NITRO. PER WEEK (TABLETS)	PETN PER 24 HRS. (MG.)	NITRO. PER WEEK (TABLETS)	PETN PER 24 HRS. (MG.)	NITRO. PER WEEK (TABLETS)
59	12	40	1	30	4
60	14	60	3	30	7
61	14	80	2	30	8
62	12	60	4	40	6
63	24	60	2	30	3
64	20	80	0	40	2
65	10	60	0	30	4
66	9	80	1	30	6
67	17	80	4	30	2
68	15	80	3	40	3
69	19	60	0	30	2
70	24	100	0	60	0
71	20	60	1	30	4
Mean	16.2	69.2	1.6	34.6	3.9
Min.	9	40	0	30	0
Max.	24	100	4	60	8

The effect of large and small doses of PETN orally on the nitroglycerin requirement was studied in thirteen patients (Table VIII). The period of observation for the controls during which no PETN was administered, and for the large doses of PETN, and for small doses of PETN was three months each. Before PETN, an average of 16.2 nitroglycerin tablets was used per week. Patients receiving the large dose of PETN (average of 69.2 mg. per day) used an average of 1.6 nitroglycerin tablets per week. These same patients when placed on a smaller dose (average of 34.6 mg. PETN per day) used an average of 3.9 nitroglycerin tablets per week.

Studies of the prophylactic effect of PETN were also made in comparison with another long-acting organic nitrate. Nitroglycerin requirements were determined in twelve patients during a 3-month control period when no other coronary dilator was employed, during administration of 30 mg. of PETN daily for 3 months, and during a 3-month period on 10 mg. per day of triethanolamine trinitrate[11,12] (Table IX). Average recommended doses of the two drugs were employed. The average number of nitroglycerin tablets used during the control

period was 12 per week; after PETN the average nitroglycerin requirement was 2 tablets per week, and after triethanolamine trinitrate the average was 6.6 tablets per week.

TABLE IX. EFFECT OF ORALLY ADMINISTERED PETN AND ORALLY ADMINISTERED TRIETHANOLAMINE TRINITRATE ON THE NITROGLYCERIN REQUIREMENT OF PATIENTS WITH ANGINA PECTORIS

	NITROGLYCERIN REQUIREMENT IN TABLETS PER WEEK		
PATIENT NO.	CONTROL—NO DRUG	PETN	TRIETHANOLAMINE TRINITRATE
72	9	2	5
73	7	1	4
74	14	3	10
75	12	2	10
76	8	2	6
77	10	1	6
78	9	0	9
79	10	1	0
80	15	3	12
81	24	6	12
82	17	1	5
83	9	2	0
Mean	12.0	2.0	6.6
Min.	7	0	0
Max.	24	6	12

DISCUSSION

The results indicate that coronary dilatation in the anesthetized dog generally occurs following the sublingual administration of PETN. This increase in coronary flow is accompanied by a slight decrease in blood pressure with little change in pulse rate. These findings are substantial evidence of coronary vasodilatation. Nitroglycerin, by contrast, produced a much larger decrease in blood pressure with a slight decrease in blood flow. This likewise is evidence of coronary vasodilatation. Others have found a consistent increase in coronary blood flow using various methods, employing nitroglycerin and other nitrites and nitrates.[4-12] In addition, there is evidence that PETN produces an increased force in the cardiac contraction as shown by the increased amplitude of the I-J wave in the ballistocardiogram. These findings are similar to those of Wégria and associates[13] and are in keeping with the findings of Lindhard,[14] who noted that after the administration of amyl nitrite cardiac output increased as long as the blood pressure remained relatively constant. Gaisböck and Jarisch noted similar effects following the subcutaneous injection of sodium nitrite.[15] The increased coronary blood flow after PETN without material effect on blood pressure or pulse rate (coronary artery dilatation) which was observed in animals explains adequately the increased exercise tolerance and decreased nitroglycerin requirement observed among patients with coronary artery disease treated with PETN. The studies also show that PETN is ab-

sorbed readily from the buccal mucosa, resulting in coronary artery dilatation. Both the animal and human data show that nitroglycerin is absorbed more rapidly than PETN by sublingual administration. However, sublingual PETN is considerably more rapid in action than is PETN administered by the usual oral route, which requires about 1.5 hours to show a significant effect.[3] The clinical trials which were carried out in an attempt to treat acute angina pectoris by sublingual administration of the drug showed that with the milder attacks of angina pectoris the attack would subside spontaneously before PETN had become effective. This was revealed clearly by the high percentage of patients who felt that their attacks of angina pectoris were relieved by placebos in the same length of time as relief was obtained with 20 mg. of PETN sublingually. Nitroglycerin 1/150 grain, however, relieved the attacks earlier and more completely than did either the placebo or PETN. Patients having attacks of angina pectoris lasting usually for 10 minutes or more were especially good subjects for these tests. Among these patients nitroglycerin was more rapidly and more completely effective than was PETN. Sublingual PETN was effective, however, in delaying and attenuating attacks of angina of effort and proved useful clinically when given 20 minutes prior to exercise such as walking to work in the morning. It was also useful when given before meals to prevent postprandial angina.

The drug proved to have very little peripheral vasodilating effect in the doses employed. The temperatures of the fingers and toes, the height of the pulsations, and relative blood flow of the digits showed only slight increases as compared to the increases which resulted from indirect body heating. These findings suggest that the drug would not be effective for the treatment of peripheral vascular disease.

Studies with other modes of administration, for example, inhalation of PETN dust, showed that large doses, that is 19 mg. inhaled, are capable of controlling acute attacks of angina pectoris. It was found, however, that patients preferred the sublingual administration of nitroglycerin as there was less effort involved in taking the drug in this manner. The studies reveal likewise that large oral doses (average dose of 69 mg. daily) are more effective in reducing the nitroglycerin requirement than small doses (34.6 mg. per day). The incidence of headaches was not increased significantly with the larger doses. This might be because the small doses in this study were given first, after which larger doses were administered.

Studies on the comparative effectiveness of small doses of PETN with triethanolamine trinitrate showed that PETN is more effective in reducing the nitroglycerin requirement than is triethanolamine trinitrate.

CONCLUSION

The sublingual administration of PETN was studied to determine if it was absorbed by this route and to determine the effect on the cardiovascular system of man and dogs. In dogs the coronary blood flow increased significantly, with a slight decrease in blood pressure without significant alteration of pulse rate.

These changes indicate the presence of coronary vasodilation. In man the pulse rate increased slightly without significant change in blood pressure. The I-J wave of the ballistocardiogram increased slightly. There was only minimal increase in skin temperatures, height of pulsations, and relative blood flow of the digits. An increase of slightly more than 2 minutes in exercise tolerance was observed. The agent was absorbed as a dust by the pulmonary epithelium. Orally, PETN was more effective in large doses (69 mg. per day) than in small doses (34.6 mg. per day). It was likewise more effective for the prophylaxis of angina pectoris in small oral doses than was 10 mg. of triethanolamine trinitrate per day.

CONCLUSION IN INTERLINGUA

Le administration sublingual de tetranitrato de pentaerythritol esseva studiate pro determinar si le droga esseva absorbite per iste via e pro determinar su effecto super le systema cardiovascular de homines e canes. In canes le fluxo sanguinee del arteria coronari esseva significativemente augmentate. Un leve reduction del pression sanguinee esseva observate sin significative alteration del pulso. Iste observationes indica vasodilatation coronari. In homines le pulso se augmentava levemente sin cambiamento significative del pression sanguinee. Le ballistocardiogramma monstrava un leve augmento del unda I-J. Minime augmentos esseva observate in temperatura del pelle, altitude del pulsation, e fluxo relative del sanguine in le digitos. Un augmento de pauco plus que duo minutas occurreva in le tolerantia a exercitio. Le agente esseva absorbite in forma de pulvere per le epithelio pulmonar. In le administration oral tetranitrato de pentaerythritol esseva plus efficace in large doses (69 mg per die) que in parves (34,6 mg per die). In le prophylaxis pro angina de pectore parve doses oral de illo se monstrava plus efficace que 10 mg per die de triethanolaminatrinitrato.

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A TECHNIQUE FOR RECORDING CAROTID ARTERY PULSATIONS WITH SPECIAL REFERENCE TO AORTIC STENOSIS

J. E. SMITH, M.D.*

WASHINGTON, D. C.

THE modern era of cardiovascular surgery has produced a demand for accurate diagnosis in various cardiovascular conditions that has exceeded the possibilities and capabilities of clinical judgment alone. Intense interest is being created in general problems of hemodynamics pioneered so soundly by Wiggers. Modern instrumentation, with the wide development of accurate electronic equipment, can easily be applied to routine clinical conditions. In diseases of the aortic valve such as stenosis and insufficiency, the surgeon will request, if not demand, to know whether a lesion is predominantly a stenotic orifice or a regurgitant orifice; or if both lesions are present, he must know which lesion predominates. Thus, any method that can make this problem simpler and diagnosis more certain will be of value. For these reasons, a study of recording carotid artery pulsations has been attempted with adaptation of instrumentation to the demands of aortic stenosis. These studies were made on the carotid artery pulsations from the skin surface, since this technique is simple and readily adapted to routine clinical use.

Wiggers[1] has stated that aortic stenosis results in a small pulse initiated by a brief sharp rise which is succeeded by a sharp anacrotic incisura. This, in turn, is followed by a slowly rising plateau upon which murmur vibrations are superimposed. Wiggers has also implied that these tracings may be difficult to reproduce clinically, since he states that "Although these phenomena are stressed in textbooks as classical signs, the anacrotic phenomenon is a rather rare clinical entity and occurs only when stenosis is severe and uncomplicated by insufficiency."[2] Goldberg and associates,[3] using brachial artery pressure curves with a Cournand-type needle and electromanometer, showed that these pulse contours were valuable in the diagnosis of aortic stenosis but found that form changes with double peaks were present in some cases. They stated that the peripheral pulse curve is practically always free of the vibrations beyond the anacrotic notch or slur. Katz and associates[4] showed that an anacrotic notch followed by multiple vibrations is observed on the central aortic pressure curve obtained in experimentally produced aortic stenosis in dogs. It seems probable that most, if not all, significant lesions which produce stenosis of the aortic orifice will have anacrotic vibrations, but differences of technique and

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*Assistant Clinical Professor of Medicine, George Washington University Medical School, and Chief, Medical Standards Branch, Civil Aeronautics Administration.

inadequate instrumentation have made the graphic registration of anacrotic vibrations difficult to reproduce easily. Thus, a technique which produces the anacrotic vibrations of aortic stenosis with high amplitudes would have great clinical utility, especially so, if the technique is simple and readily adaptable for routine clinical use.

INSTRUMENTATION AND TECHNIQUES

The carotid artery is easily accessible and close to the centrally generated vibrations in aortic stenosis, and subsequent discussion is limited to application of recording pulsations through the skin and subcutaneous tissue over the carotid arteries in the neck.

A cup placed over the carotid artery and sealed tightly can be used. The most satisfactory cup application has been a wooden, halter-type neckpiece that has an adjustable clamp so that it can be applied firmly and left in place without changes in position for relatively long periods of time. This type of wooden compressible neck clamp is available commerically.* From the cup on the neckpiece, a piece of thin, flexible rubber tubing of $\frac{1}{16}$-inch inside diameter is led into a crystal-type pickup which produces an electrical signal proportional to pressure changes in the tubing. The crystal used is also available commercially† and has a condenser inserted to improve the low-frequency response of the crystal output. The high-frequency response of this type of crystal is excellent and flat to beyond 200 cycles.

Initial studies with this type of instrumentation were done with a tubing length of 8 feet. This length of tubing was found to have a time lag of 0.015 sec. due to tubing transmission factors, but initial studies of cases of aortic stenosis showed high-amplitude vibrations on pulse contours that could be changed by changing the length of tubing. From these data, it was immediately obvious that the physical properties of the vibrating air column in a system of elastic tubing might influence the total system response, and thus an analysis of the resonant frequency of the tubing was found to be important. Analysis of the frequency components of the recorded anacrotic vibrations from aortic stenosis pulse contours indicated that these vibrations were between 40 and 80 cycles in frequency, and thus the type of recorder would also become an important consideration as many direct-writing recorders have a flat response to about 30 cycles and would obscure components of higher frequency.

From previous clinical experience in using signal differentiation in ballistocardiography, it would seem likely that signal differentiation would be useful in this type of problem to emphasize higher-frequency components of physiologic significance. Noble[5] has previously indicated that the clinician might utilize the principles of signal differentiation to advantage in many clinical problems. Electrical differentiation, while feasible, had many disadvantages due to loss of signal in differentiation and the susceptibility to ambient noise pickup inherent in the design of electrical differentiators. Preliminary studies

*Cambridge Instrument Company, Inc., New York 17, N. Y.

†Sanborn Company, Cambridge, Mass.

of the system of elastic tubing showed that it would be simple to adapt the resonant frequency of the vibrating air column in such a way that a crude but effective differentiation of the signal could be done. This method is of advantage in that it would be cheap and practically free of ambient noise so commonly found in electrical circuits. Studies on a tubing length of 8 feet showed a flat resonant peak between 30 and 40 cycles. Since the resonant peak is related to the tubing length and doubles when the tubing length is halved, a resonant peak at about 70 cycles could be obtained with a tubing length of 4 feet. Clinical

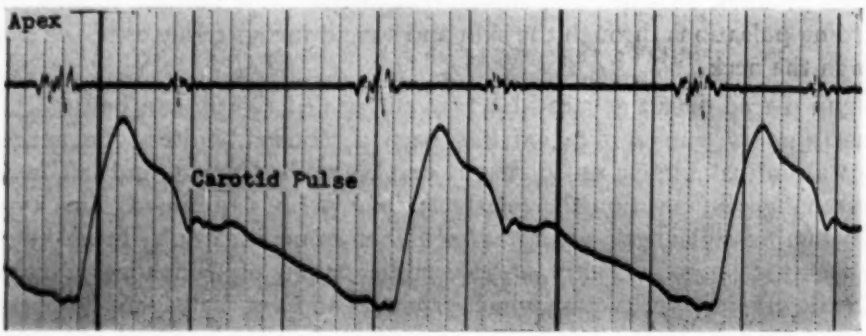

Fig. 1.—Carotid pulse tracing on a normal 28-year-old male medical student, 75 mm./sec. paper speed.

studies indicated that a tubing length of 4 feet would seem to be ideal as the signal lag (due to tubing transmission) was under 0.01 sec. and pulse-amplitude contours in normal individuals showed little attenuation (when compared to 2 inches of tubing length), and anacrotic vibrations showed no detectable decrease in amplitudes (when compared to 8 feet of tubing length). Thus, a simple type of differentiation could be accomplished by utilizing the resonant frequency of the tubing. This type of apparatus as described will yield a nonlinear response with resulting phase distortion, but this would seem to have little clinical significance, since aortic stenosis seems to be the only disorder in which vibrations of this frequency have been found. This technique is, in essence, the application of a simple Helmholtz resonator. A normal carotid pulse in a 28-year-old medical student is illustrated in Fig. 1.

CLINICAL MATERIAL AND CASE REPORTS

The clinical material studied was sixteen cases of aortic stenosis, twelve were considered to be cases of "pure" stenosis of the aortic valve, two cases of aortic stenosis and concomitant aortic insufficiency, and two cases of aortic stenotis and probable mitral stenosis.

CASE 1.—A 19-year-old Negro was referred for study by the Army Induction Board. A heart murmur had been detected five years previously during a school examination. There was no history of rheumatic fever. He had no symptoms and had been doing heavy construction work without difficulty.

Examination showed a well developed and nourished young male with no signs of congestive failure or clubbing. Blood pressure 110/70 mm. Hg. Heart examination revealed a loud, harsh

systolic murmur over the entire precordium, heard loudest at the aortic area, Grade 4, accompanied by a palpable thrill. Murmur was also loud at the mitral area. A_2 was not diminished. Rhythm was regular, rate 88. The electrocardiogram was normal. Fluoroscopy showed the left ventricle concentric in shape, otherwise entirely normal. No evidence of valve calcification. The ballistocardiogram was normal.

Clinical diagnosis: Aortic stenosis, asymptomatic, etiology undetermined. Possible subaortic stenosis.

The carotid pulse tracing is illustrated in Fig. 2. The anacrotic notch and succeeding vibrations are easily seen with high amplitudes. The phonocardiogram was taken at the aortic area and shows a diamond-shaped configuration with variable forms.

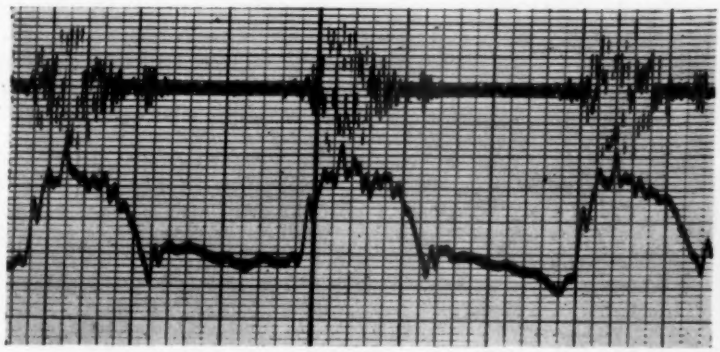

Fig. 2.—Phonocardiogram and carotid pulse tracing on a 19-year-old male (Case 1) with clinical evidence of aortic stenosis. 75 mm./sec. paper speed.

CASE 2.—A 29-year-old Negro was admitted to the George Washington University Hospital on March 3, 1954, with a diagnosis of anemia and heart murmur. For two weeks prior to admission, this patient had several syncopal episodes, headaches, and fever. He had received some antibiotic therapy by a private physician prior to admission. There was no history of rheumatic fever, and general health had been good until onset of the present illness. He had been advised of the presence of a heart murmur two years previously.

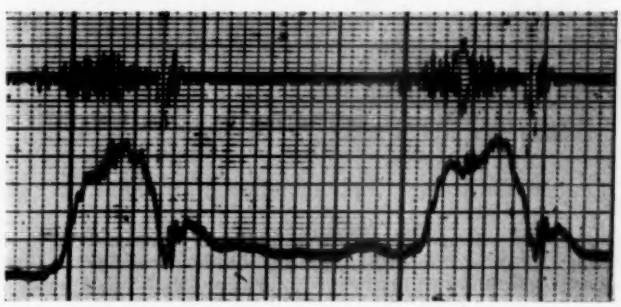

Fig. 3.—Phonocardiogram and carotid pulse tracing of a 29-year-old male (Case 2) with clinical evidence of aortic stenosis. 75 mm./sec. paper speed.

On admission this patient was afebrile. Blood pressure was 95 65 mm. Hg. A loud systolic murmur, Grade 4, was heard with maximal intensity at the aortic area with a palpable thrill but

was also heard over the entire precordium. There were no signs of congestive failure. A marked normocytic hypochromic anemia was found. Hemoglobin, 5.7 grams. Blood cultures (9) were consistently negative. The electrocardiogram showed RS-T segment changes consistent with left ventricular strain. The ballistocardiogram was of low amplitude with large N waves but minimal form abnormality. Anemia was corrected with transfusions, and the murmur decreased in intensity, Grades 2 to 3. Since discharge he has returned to work and has remained entirely asymptomatic.

Clinical diagnosis: Aortic stenosis, etiology undetermined.

The carotid pulse tracing is illustrated in Fig. 3, with phonocardiogram taken at the aortic area.

CASE 3.—A 48-year-old white male was admitted to George Washington University Hospital with substernal pain and acute pulmonary edema. He responded well to treatment. Examination showed blood pressure of 110/80 mm. Hg with a Grade 4, harsh systolic murmur at the aortic area with a palpable thrill. The murmur was transmitted over the entire precordium. A_2 was indistinct. The electrocardiogram showed nonspecific ST-T changes. Fluoroscopy revealed left ventricular enlargement. No calcification could be seen. VDRL, 3 plus. Kahn, negative.

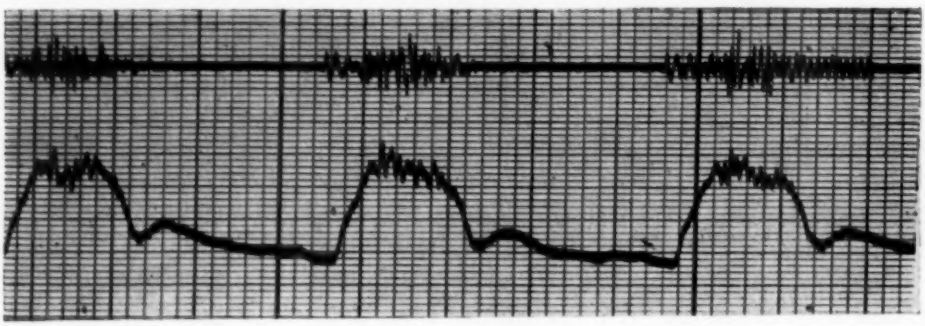

Fig. 4.—Phonocardiogram and carotid pulse tracing in a 48-year-old male (Case 3) with clinical evidence of aortic stenosis. 75 mm./sec. paper speed.

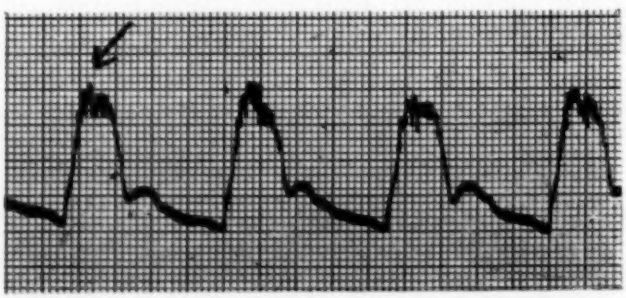

Fig. 5.—Pulse tracing on same patient (Case 3) as Fig. 4. This was taken at 25 mm./sec. paper speed on a direct-tracing type of recorder with limitation of frequency response (flat to 30 cycles). Note the tendency of anacrotic vibrations to produce a double-summit type of curve.

Clinical diagnosis: Aortic stenosis, etiology undetermined.

The carotid pulse tracing is illustrated in Fig. 4. This case showed double-summit type curves when recorded on an oscilloscope with the frequency response flat to only 20 cycles. This tendency to show double peaks in this case is present on a direct-tracing recording and is illustrated in Fig. 5.

CASE 4.—A 38-year-old white female with a history of rheumatic fever at the age of 6 and a recurrence at the age of 13. This patient had two pregnancies without difficulties in 1945 and 1951. She continues to be asymptomatic except for some fatigability. Blood pressure was 155/60 mm. Hg. Point of maximal impulse was present at the sixth intercostal space at the anterior axillary line. Pulse 72, regular. A loud, harsh systolic murmur, Grade 4, was present in the aortic area with a palpable thrill. A_2 was present. A Grade 3 blowing diastolic murmur was present, heard best at the third left intercostal space. Both murmurs could be heard over the entire precordium. The ballistocardiogram showed high amplitudes and, predominantly, form changes of aortic insufficiency. The electrocardiogram showed evidence of left ventricular hypertrophy. Fluoroscopy showed evidence of left ventricular enlargement.

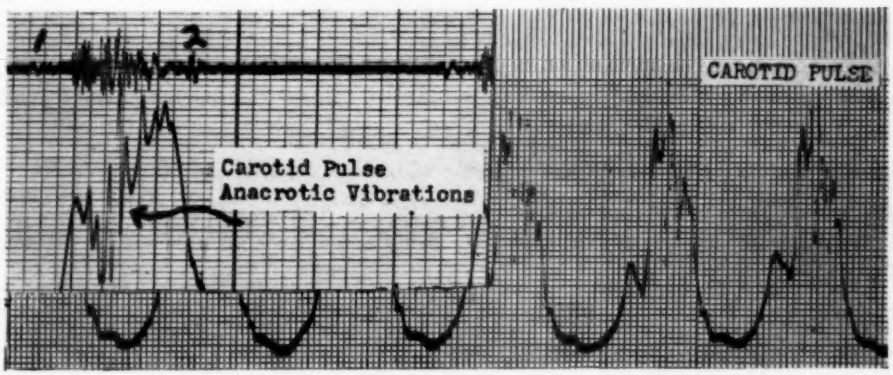

Fig. 6.—Pulse tracing on a 38-year-old female with clinical aortic stenosis and aortic insufficiency. Note the extremely high-amplitude anacrotic vibrations. The insert was taken on a galvanometer of high response (flat to over 200 cycles) at 75 mm./sec. paper speed. Note also the loss of configuration of the period of isometric contraction and dicrotic notch.

Clinical diagnosis: Rheumatic heart disease, inactive, with enlarged heart and aortic stenosis and insufficiency. Asymptomatic.

The carotid pulse tracing is illustrated in Fig. 6.

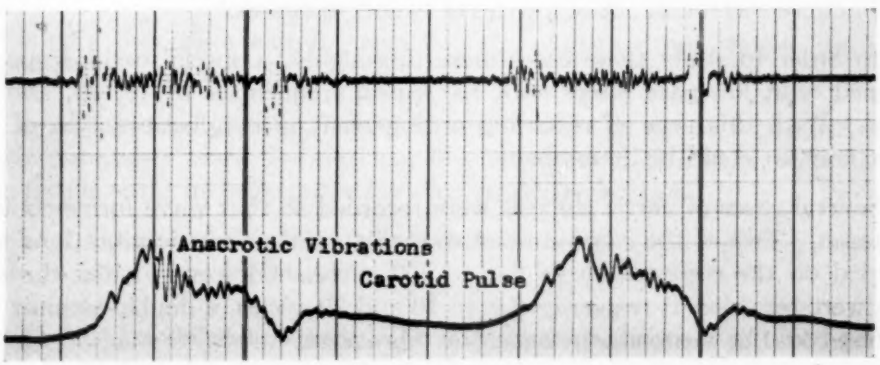

Fig. 7.—A 24-year-old female (Case 5) with clinical diagnosis of aortic stenosis and mitral stenosis. The carotid pulse shows high-amplitude anacrotic vibrations with markedly prolonged anacrotic slope.

CASE 5.—A 24-year-old Negro woman with a history of rheumatic fever at age 12 and a recurrence at 15. She noticed the onset of mild dyspnea on exertion at the age of 17. During

pregnancy at the age of 21, she developed 2-pillow orthopnea but no complications during delivery. She was told then of a "heart" condition.

At the time of examination in July, 1954, she complained only of mild exertional dyspnea on climbing one flight of stairs or walking one city block. There is no evidence of failure, but she sleeps on two pillows and can do only light housework due to fatigue and dyspnea.

Examination revealed blood pressure of 90/60 mm. Hg, forceful point of maximal impulse in the fifth intercostal space at mid-clavicle. Rate was 78. P_2 was moderately accentuated. An opening snap was heard best at the third left intercostal space. A loud, harsh, Grade 4 to 5 systolic murmur could be heard at the aortic area with a palpable thrill transmitted into the neck. Also, a Grade 3 blowing diastolic murmur could be heard at the third left intercostal space. At the apex, a booming M_1 with a loud Grade 3 rumbling diastolic murmur was heard. The electrocardiogram showed high-amplitude notched P waves. The ballistocardiogram showed extremely low amplitudes with notching of acceleration J peaks and prolonged displacement IJ slopes. Fluoroscopy showed a mitralized heart with prominent pulmonary artery, with evidence of both right and left ventricular enlargement.

Clinical diagnosis: Rheumatic heart disease with aortic stenosis and mitral stenosis.

The carotid pulse in this case is illustrated in Fig. 7. The anacrotic vibrations are of high amplitude and, in general, the amplitudes of vibrations varied in the same manner as the murmur recorded at the aortic area.

DISCUSSION

It was of interest that in this group of cases of aortic stenosis, there were no cases showing the double-summit type of pulse tracing when recorded on a high-frequency galvanometer system (flat to over 200 cycles) and a fast-paper speed (75 mm./sec.). In a series of cases reported by Feil and Gilder,[6] the double-summit pulse tracings were found more frequently than curves having anacrotic vibrations.

In the cases reported by Goldberg and associates[3] from the brachial artery, the usual type of curve in aortic stenosis was one with an anacrotic slur or notch with delayed peaks, but they reported eight cases in which a double-summit type of curve was found out of a series of twenty-six cases.

In order to study these cases more thoroughly, a special oscilloscope was designed with low-pass filters with flat cutoff frequencies of 10, 20, and 300 cycles. With this type of recording arrangement, a rough estimation of harmonic content could be determined.

Several cases of aortic stenosis were recorded so that wave forms could be compared. Two of the cases studied showed typical anacrotic vibrations when recorded on the response curve flat to 300 cycles. However, when the same cases were recorded at responses flat to 10 and 20 cycles, a double-summit type of curve could be seen without anacrotic vibrations.

Thus, any recorder (or technique), when used to record curves having a frequency content higher than the cutoff frequency of the recorder, will average the higher-frequency components and thus give the appearance of double peaking, rather than the true vibratory phenomena.

From these observations, it is suggested that some, if not all, of the double-summit peaks found in aortic stenosis may be due to inadequate techniques or instrumentation, and thus should be carefully evaluated before any physiologic significance could be attempted. Also, the paper speeds of recorders are important since some vibrating phenomena of low amplitudes will be obscured at 25 mm./sec. but can be seen readily at 75 mm./sec.

In this study, there seemed to be no direct relationship of the amplitudes of anacrotic vibrations to severity of the stenosis. While this is extremely difficult to quantitate, the analysis of functional ability and the ballistocardiograph would indicate that the compensatory myocardial factors are as important as the severity of the stenosis in the production of these vibrations. In other words, it is suggested that the amplitudes of recorded vibrations are related to the ability of the left ventricle to accelerate blood forcefully, and thus the forces generated during ventricular systole against a stenotic orifice play an extremely important part in the amplitudes of anacrotic vibrations. These factors seem to be as important as the severity of the stenosis in the cases studied.

SUMMARY AND CONCLUSIONS

1. Simple techniques for recording carotid artery pulsations from the body surface have been described.

2. The utilization of the natural frequency of an air column in a system of closed elastic tubing can be used to emphasize the anacrotic vibrations of aortic stenosis when adjusted to the proper frequencies.

3. The importance of techniques and recording instrumentation have been emphasized.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Es describite simple technicas pro registrar pulsationes del arteria carotide ab le superficie del corpore.

2. Le frequentia natural del columna aeree in un systema claudite de tubo elastic pote esser usate pro clarificar le vibrationes anacrotic de stenosis aortic si on face le requirite adjustamentos al correcte frequentias.

3. Le importantia de un ben-elaborate technica e un precise instrumentation registratori es sublineate.

Grateful acknowledgment is made to Frank W. Noble, biophysicist, National Institutes of Health, for his analysis of the tubing used in this study.

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STUDIES IN ANGIOCARDIOGRAPHY: THE PROBLEM OF INJECTION

Presentation of a High-Pressure Automatic Injecting Machine to Meet the Needs of Modern Angiocardiography

Antonio Rodríguez-Alvarez, M.D.,* and
Narno Dorbecker, M.D.**

Mexico City, Mexico

WORK at the National Institute of Cardiology in the last few years has been hampered by the lack of selective angiocardiographic studies as well as by the low contrast of our aortograms. In order to keep pace with the rapid development in the surgery of the heart and great vessels we have found it necessary to revise our methods.

The first hurdle was the problem of adequate injection through long narrow-bore cardiac catheters as used by the Swedish workers. We discovered this to be the most urgent problem after studying many of the techniques more commonly used for the injection of contrast media. We wish to present first a brief review of angiocardiographic methods from the point of view of the basic physical principles pertaining to the flow of fluids through catheters in order to evaluate their usefulness in relation to modern cardiovascular advancements.

In the pages to follow the "injecting system" shall designate any mechanical or manual means of injecting the radiopaque substance. The "connecting system" shall be the needles, tubes, or blood vessels by means of which the radiopaque substance flows from the injecting mechanism to the "organ-host". The "organ-host" is readily understood to be any particular segment of the cardiovascular system under study.

The techniques so far developed for angiocardiography may be analyzed from three different points of view: (a) the mechanism utilized for injecting the radiopaque substance; (b) the connecting system, and (c) the "organ-host". Other important features of angiocardiography such as radiopaque substances, radiologic techniques, thorough study of the patient, determination of circulation time, etc., all require careful consideration but fall outside the scope of this paper. We will examine in detail the basic principles underlying the various types of injecting mechanisms and connecting systems. Certain aspects of

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*Research fellow in angiocardiography and hemodynamics at the Instituto Nacional de Cardiología de México.

**Chief of the Department of Radiology at the Instituto Nacional de Cardiología de México.

the different "organ-hosts" will also be dealt with. Finally, we will present the working details of an entirely automatic high-pressure injecting maching'

From the point of view of the injecting mechanism and the connectine system, all methods developed for angiocardiography can be divided into two main groups: (a) those using connecting systems of low-flow resistance (short and wide-bore needles[1,2]; short and wide-bore rubber tubes[3-5]) which by the very nature of the system do not require injecting mechanisms of high pressure; and (b) those using connecting systems of high-flow resistance (long, wide-bore needles[6-10]; long, thin-bore cardiac catheters Cournand type[11-17]; long thin-bore polyethylene catheters[18]) that by the nature of the system require injecting mechanisms of high pressure.

This grouping is based on Pouiseille's law, which correlates the factors that determine the circulation of fluids in a system of tubes. This law states that resistance to flow increases in proportion to the length of the connecting system and is inversely related to the square of the cross-section area of the tube. The mathematical expression of resistance would be:

$$R = \frac{lv\,8\pi}{q^2}$$

where R is resistance, l is the length of the connecting system, v is the coefficient of viscosity of the fluid, $8\,\pi$ is a constant, and q^2 is the square of the cross-section area of the connecting system.

If we apply this law to the connecting system, v refers to the viscosity of the radiopaque media, which is similar for the different commercial brands at the same concentration. Furthermore, viscosity must remain constant if concentration is to be kept at the level of the optimal radiopacity. Since $8\,\pi$ is another constant, only l (length of the connecting system) and q^2 (square of the cross-section area) remain as factors capable of modifications. The variation of these two factors will be regulated by the anatomic, functional, and diagnostic needs of each individual case.

Ideal angiocardiography must fulfill at least the following requirements: (1) it must be harmless; (2) it must be easy to perform; (3) it must provide clear contrasting visualization of the "organ-host"; (4) it must give information concerning the times of arrival of the radiopaque substance at the "organ-host" and of persistence of the opacity within this host; (5) it must be easy to repeat under the same conditions for control studies.

Some angiocardiographic methods may be highly efficient, yet they are dangerous or difficult to perform. Preference should then be given to others which may be less accurate but which are simpler and less traumatic. Good angiocardiography is based on good x-ray plates obtained at the optimal moment, and these depend on many factors, some of which are (1) adequate concentration of radiopaque substance in the blood of the "organ-host", (2) exact timing of x-ray exposures in relation to the moment of injection and of the cardiac cycle; (3) adequate x-ray penetration which can be increased in proportion to the degree of contrast obtained by correct concentration of the radiopaque substance thus permitting the elimination of undesirable and unnecessary shadows;

(4) thorough appraisal of known and inferred hemodynamic data in each case, since the speed of injection of the radiopaque substance as well as the direction and the velocity of the blood within the "organ-host" must be intelligently considered; an example would be the rate of blood clearance in every segment of the cardiovascular segment; (5) correct positioning of the patient in order to obtain the most favorable view of the "organ-host", or the use of biplane x-ray.

On the basis of the foregoing discussion, an analysis of some of the most representative angiocardiographic methods will be presented. Castellanos and associates[1] have used a method which consists in the injection of the radiopaque substance into a vein of the antecubital space by means of an ordinary glass syringe and needle (a Lindeman or Becton Dickinson needle for blood transfusion). In this technique, the connecting system is formed by the needle and the vein up to their opening into the "organ-host". This method has been used in infants with good results, since the low-flow resistance of their connecting system allows for a rapid injection, and the radiopaque substance arrives in good concentration at the "organ-host," in spite of the inevitable dilution that takes place. This method is relatively harmless and easy to perform. However, it lacks selectivity and correct timing is sometimes difficult to obtain due both to the unpredictability of the distance that the substance has to travel from the site of injection to the "organ-host", and of the velocity of the blood stream.

Robb, Steinberg, and Dotter[2,20] introduced a similar method for angiocardiography in adults. They used a modified Lindeman transfusion needle, (Steinberg's needle) 12 gauge, with a specially constructed 50 c.c. glass syringe which has a tip-bore equivalent in caliber to that of the needle used. They also added two devices which tend to facilitate the progression of the radiopaque substance: (a) elevation of the patient's arm to about 45° above the horizontal (patient sitting down before the x-ray machine); (b) the patient is instructed to make a deep inspiration during the injection.[20] They introduced the routine determination of circulation time prior to the injection of radiopaque substance. With these refinements they obtained excellent results especially in regard to the right cardiac chambers.

Other disadvantages, however, still persist, and these include increased dilution of the radiopaque substance due to the distance at which it is injected from the "organ-host". The low concentration obtained at the level of the "organ-host" hampers the use of high x-ray penetration techniques with a resulting poor visualization. Attempts to obtain good visualization of the aorta by injecting the radiopaque substance into the veins of the antecubital space are unsuccessful since the aorta is obscured by other previously opacified structures. Clear visualization of the secondary filling of the pulmonary artery by this technique in cases of patent ductus arteriosus has failed.[21] Chemical thrombosis of the injected veins occurs in an estimated 80 to 90 per cent of the cases. In rare instances frank thrombophlebitis has been reported.[20] The popularity of this method is readily explained when we consider the simplicity, economy, and relative harmlessness.

Robb and Weiss's[22] skillful methods for the determination of the circulation time were later applied by Robb and Steinberg to angiocardiography. Their methods improved the study of abnormal morphology and dynamics of the heart and great vessels.

A different connecting system was suggested by Egas Moniz and associates,[13] and used by Perez Ara,[3] and Celis[4] for the purpose of opacifying the pulmonary vessels. Chávez and associates[5] in 1947 applied this technique to the study of cardiovascular structures. In order to inject the radiopaque substance, dissection of the external jugular vein is performed and a No. 12 or 14 Nelaton catheter is introduced into the right chambers of the heart under fluoroscopic control. Circulation time is previously determined. Injection of 50 to 100 c.c. of 70 per cent Diodrast is performed by means of an ordinary glass syringe. Injection is made by hand as rapidly as possible, usually in one and one-half seconds. The authors recommend deep penetration techniques for x-ray exposures, which can be done without loss of detail within the heart chambers and great vessels due to the high concentration of the radiopaque substance.

The advantage of this method is the speed of the injection, which is possible without special equipment because of the very low-flow resistance of the connecting system. Thus, contrast of the right chambers of the heart is excellent. This method marked the beginning of selective angiocardiography[16] for the right chambers of the heart.

Comparative studies of this method and that of Robb and Steinberg made in the U.S.A. by Sutton and associates,[23] and in Mexico by Cahen and associates,[24] have shown that the former gives better results in the majority of cases.

Vein dissection is in itself, however, a minor surgical procedure that takes time and leaves a visible scar, which is probably one of the reasons why this method has not found a wider acceptance in other countries.

The pliability of the rubber catheter makes it extremely difficult to guide beyond the right ventricle and allows for a great backward displacement due to recoil of the tip at the moment of injection.

Selectivity, therefore, can not be controlled in all cases. Superimposition of opacified structures and dilution of opaque substance lessen the usefulness of this method in the study of the left chambers of the heart and the aorta. This last disadvantage is common to the methods using the venous system for injection. However, in spite of dilution, the aorta may be visualized. The secondary filling of the pulmonary artery by this technique in cases of persistent ductus arteriosus has been visualized in some cases.[25] As far as mortality is concerned, this method has no extra risks and with a trained team it is relatively easy to perform.

The group of methods just discussed is characterized by the injection of radiopaque substance through a connecting system of low-flow resistance. There is another group of angiocardiographic techniques in which the connecting system has a high-flow resistance.

Translumbar aortography was introduced by Dos Santos and associates

in 1929.[6] They developed and practically exhausted the possibilities of their method. By their technique 5-inch needles are used in order to reach the aorta. The relatively great flow resistance of such a connecting system needed a special injecting apparatus which they devised and which later was adopted throughout the world.

In 1941, Fariñas[26] recommended the arteriographic study of the abdominal aorta and its branches by the puncture and catheterization of the femoral artery at the triangle of Scarpa. In 1946, he adopted[27] the retrograde or counter-current method of Castellanos and associates,[19] working almost exclusively with adults and senile subjects. He used an original apparatus for the automatic high-pressure injection of the contrast solution.

Attempts have been made since 1936 to puncture the ascending aorta through the sternum or parasternally, by Nuvoli in 1936,[28] by Radner in 1945,[7] and by Gomez del Campo and Meneses Hoyos in 1947.[8] These methods have been used only in adults. In 1940, Castellanos and associates[19] solved the problem of thoracic aortography in infants by injecting the radiopaque substance against arterial blood flow. They used Lindeman needles and manually or by means of the low-pressure machine devised by Paussa[29] injected radiopaque substance directly into the brachial artery. This they were able to do because their connecting system had a low-flow resistance. They failed to obtain satisfactory aortographies when they applied their technique to children over 12 years of age.

In 1948, Radner[14] succeeded in catheterizing the proximal portion of the aorta by introducing a Cournand-type cardiac catheter through the radial artery and injecting while the tip of the catheter was a few centimeters from the aortic cusps, but he failed to obtain good concentration of the radiopaque substance because of the high-flow resistance of this long and narrow connecting system. He made the method available to Brodén and associates,[15] and they obtained the same poor plates. At the same time they stated specifically that the only solution would be to inject the radiopaque substance in less than 7 seconds. They felt that an injecting machine of high pressure would solve this problem. In 1949, Brodén and associates[17] published successful results through the use of an injecting machine devised by Jönsson.[9] Aortography was facilitated and greatly improved by this injecting mechanism of high pressure.* In the same year Jönsson and associates[16] also described methods for selective angiocardiography of the right chambers of the heart and the pulmonary artery and its branches. In cases of atrial septal defect the left chambers could also be visualized utilizing this same equipment.†

In 1933, Reboul and Racine[34] reported on experimental transthoracic "ventriculography." Recently, Ponsdomenech and Beato Nuñez[10,35] have made direct intraventricular injection of radiopaque substance by means of a 5.5-inch needle and a modified Dos Santos apparatus. So far, these authors have injected more than sixty patients without a fatality.

*Retrograde injections through the carotids were reported by Stephens[30] in 1948, Burford and associates[31] in 1949, Jönsson in 1949,[9] and Freeman in 1949.[32] In 1949, Euler[33] suggested the puncture of the aorta via the esophagus.

†Moniz and associates[13] used a similar catheter for the purpose of opacifying the pulmonary vessels.

Each one of the methods described has specific indications, but none solve all the problems of angiocardiography. Until recently (1949), a good method for thoracic aortography and for selective angiocardiography did not exist, and this was due mainly to the high-flow resistance in the long connecting system. It then became obvious that an injecting mechanism, powerful enough to overcome the high resistance and to permit rapid injection and good concentration of radiopaque substance into the "organ-host" was necessary. Dos Santos and associates[6] were aware of this important difficulty as far back as 1929. Since that time, many injecting machines have been used with more or less success. Those of outstanding importance will be described briefly under two different classifications: (1) Those in which the radiopaque substance is contained within a glass cylinder and is expelled by the pressure of an air column without an interposed plunger. The air is contained within this glass cylinder and in contact with the opaque substance. (2) Those using a glass or metal syringe and different sources of energy to operate an interposed plunger (i.e., air under pressure, oxygen under pressure, potential energy in the form of collapsed steel coils, etc.).

1. The injecting mechanism of Dos Santos and associates[6] consists of an air deposit filled by means of a bicycle pump at low pressure (3 atmospheres or 44.1 lb. per square inch). The air is released by means of a stopcock into a glass cylinder containing the radiopaque substance. The injection of opaque substance is controlled by means of another stopcock, placed at the other end of the cylinder. The operator must release the opaque substance and close the stopcock before air penetrates into the connecting system. A manometer allows quantification of pressures used and, therefore, enables one to repeat the injection utilizing identical pressures. There are two main drawbacks to this mechanism: (1) the risk of injecting harmful quantities of air into the circulatory system, and (2) the impossibility of obtaining high-injection pressures because of the low strength and fragility of the glass walls of the cylinder. These objections practically invalidate the use of this and other similar pressure machines,[36] if the modern trends of angiocardiography which require the use of high-injection pressures are to be kept. This was not the problem at the time the machine was devised. (Dos Santos needle for translumbar aortography constitutes a relatively low-flow resistance connecting system.)

2. In 1941, Fariñas[26] demonstrated an injecting mechanism consisting of a glass syringe with two plungers, one in contact with the radiopaque substance and the other with a column of air, thus obviating the possibility of injecting air into the connecting system. He utilized a larger air chamber than did Dos Santos, but his glass syringe continued to eliminate the use of high pressures. Therefore, it does not meet modern demands.

Lindgren,[37] in 1953, devised quite a similar apparatus with which 8 atmospheres (117.6 lb. per square inch) of pressure may be reached by means of a mechanical compressor. An added feature of his machine is a microswitch that closes the circuit of the seriograph and the x-ray machine.*

*This automatic switching had been used before by Paussa.[29]

The need for attaining higher pressures was felt by Brodén and associates,[15] and in 1949, Jönsson[9,16,17] presented a new injecting mechanism equipped with a metallic syringe. The mechanical energy to move the plunger is provided by a lever arm, operated by human force. To prevent the entrance of air bubbles into the circulation, a special device is used to stop the plunger before it reaches the end of its course. There is no manometric control of the pressures reached by this apparatus, but by using 8F and 9F Cournand type cardiac catheters these authors have injected 50 c.c. of radiopaque substance approximately in 6 and in 2 seconds, respectively, and obtained the most beautiful thoracic aortographies then on record.[38]

The apparent simplicity of this machine becomes less evident when one considers that the pressure of injection is not known, and therefore control studies cannot be repeated under identical pressure conditions. It is also practically impossible to maintain a uniform pressure throughout the injection and furthermore selection of pressure to be utilized in respect to catheter size would be difficult.

Another machine described by Mouquin and Durand,[39] demonstrated in Mexico in 1952, has been widely used in France. It consists of an air chamber with a loose plunger. Since the plunger is not snugly fitted to the walls of the glass cylinder, it is previously sealed with the patient's citrated blood. It is also provided with a conical rubber stopper that prevents air from penetrating into the connecting system. A microswitch controls the circuit of the excellent seriograph constructed by Durand and Coudert. Besides being cumbersome, it still has a glass cylinder and, therefore, the injection pressure obtainable is low.

In the foregoing we have shown that the best connecting systems for angiocardiography to date are also those that offer a high resistance to flow. The machines used to inject the radiopaque substance have been devised in an attempt to reach injecting pressures high enough to overcome the flow resistance and inject in a minimum of time in order to produce good concentration. The drawbacks and insecurities of the injecting mechanisms just described have led us to build a machine that will overcome the limitations imposed upon modern angiocardiographic needs.

The machine consists of two main parts: a syringe and a source of energy. The syringe (Fig. 1) is made of Swedish stainless steel and it stands with the tip pointing upward. It is made of two pieces: a hollow cylinder 2 inches in diameter (Fig. 1, *3*) with a conical dome that opens into a tip bore provided with a one-way stopcock adapted to a Luer lock tip (Fig. 2, *2*). A 3 mm. bore vinyl tube connects with the stopcock on one end and with the connecting system on the other. This tube may be lengthened at will in order to interpose a safe distance between operator and x-ray source.* The plunger is solid steel (Fig.

*The ideal transparent plastic tubing is not manufactured with the desired bore and wall thickness; we overcame this difficulty by introducing a tube of adequate bore into a wider one.

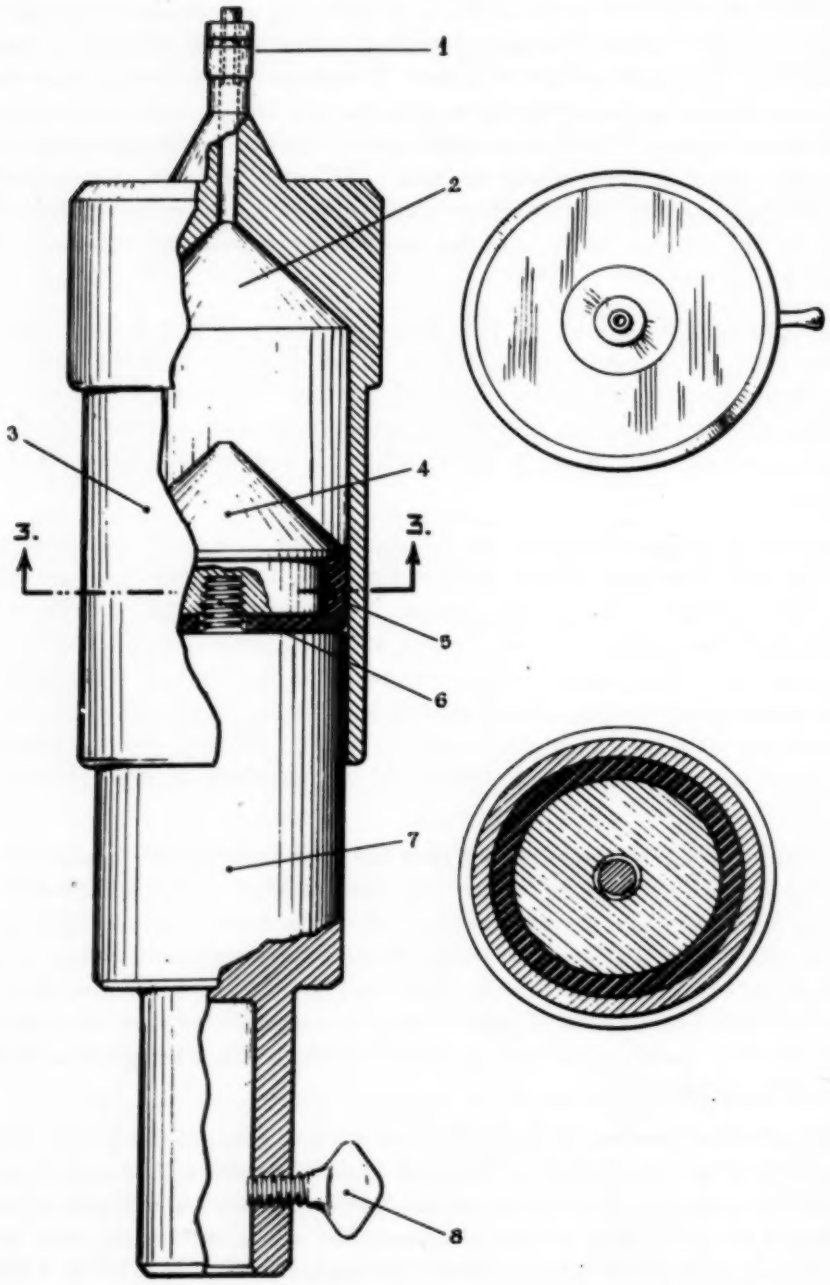

Fig. 1.—Diagram of the injecting device of the apparatus. Metallic syringe: 3, cylinder; 4, conical tip to avoid dead space; 7, plunger.

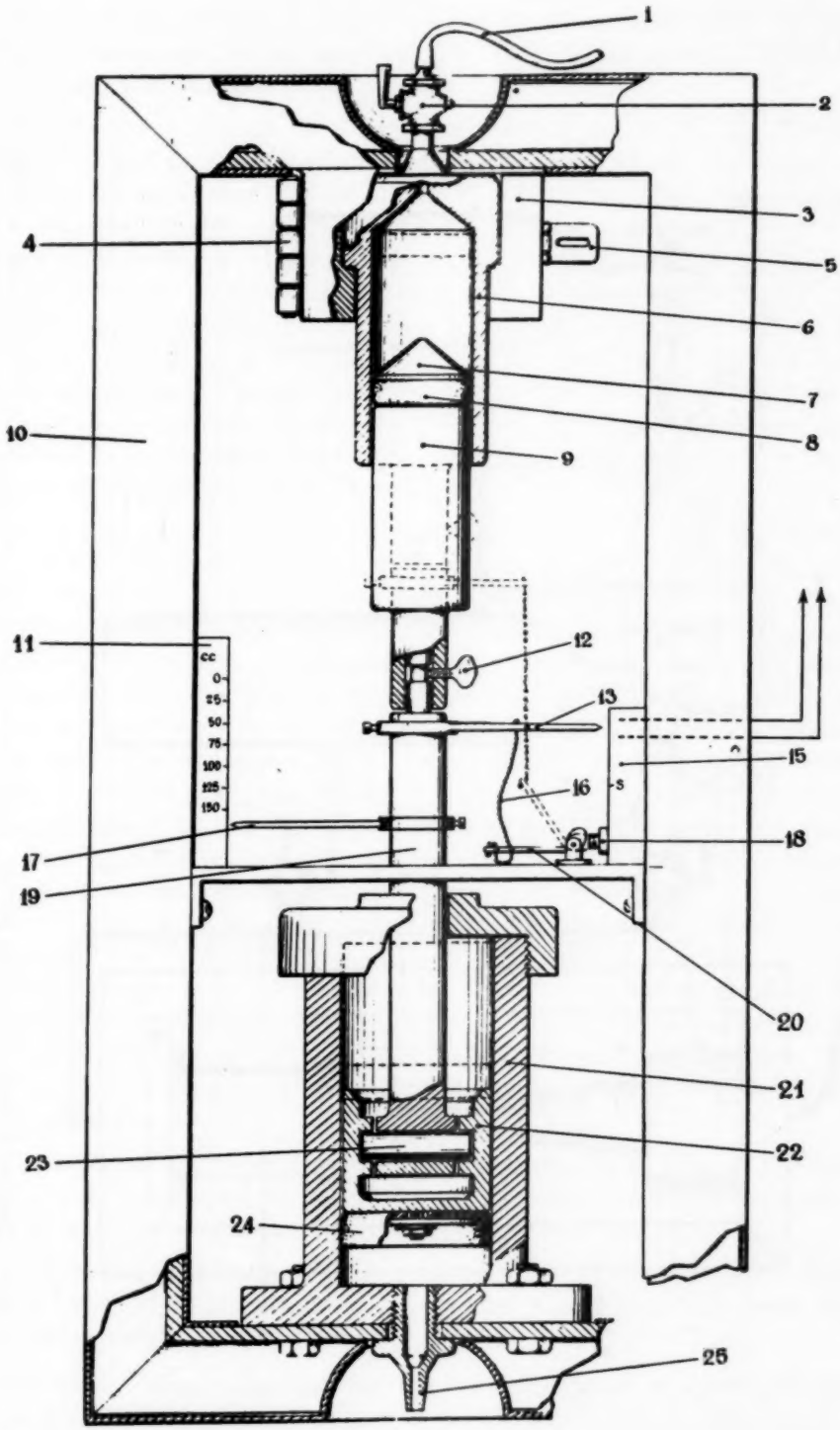

Fig. 2.—Diagram of syringe with plunger and cylinder and its piston, in steel frame. *1*, vinyl tube to connecting system; *18*, microswitch; *21*, cylinder; *22*, piston.

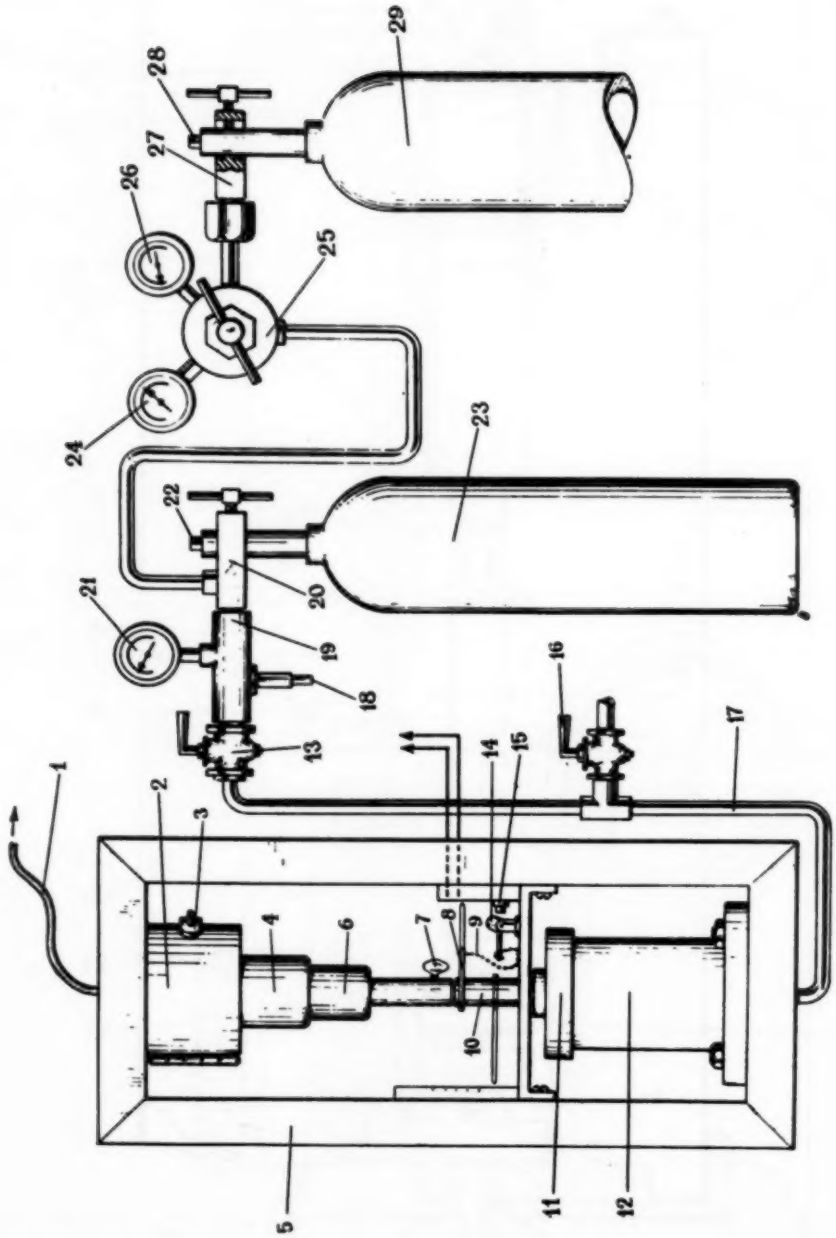

Fig. 3.—Diagram of complete injecting system. *5*, steel frame with syringe and cylinder; *16*, exhaust valve; *13*, inflow valve; *21*, second low-pressure manometer; *23*, low-pressure tank; *24*, first low-pressure manometer; *25*, demand regulator; *26*, high-pressure manometer; *29*, container with commercial compressed air.

1,*7*), loosely fitted into the cylinder. An inch and one-half below the tip there is a round cup-shaped rubber packing (Fig. 1, *5*), which seals the space left between plunger and cylinder.

The plunger is topped by a conical piece (Fig. 1, *4*) that fits the dome of the cylinder and practically eliminates dead space. In the lower part of the stem of the plunger there is a set screw (Fig. 1, *8*) that fixes the plunger to the piston stem (Fig. 2, *19*). Contained within another hollow cylinder (Fig. 2, *21*) 4 inches in diameter is a piston (Fig. 2, *22*) connected to the plunger. This piston is driven by means of compressed air. Attached to the piston stem is a ring with a pointer (Fig. 2, *13*), joined to a lever by means of a chain (Fig. 2, *20*), which operates a microswitch (Fig. 2, *18*), connected through two wires with the seriograph. There is another pointer (Fig. 2, *17*), attached to the piston stem, and a scale calibrated from 0 to 150 which indicates the number of cubic centimeters of radiopaque fluid to be injected. All these different parts are contained within and supported by a strong steel frame (Fig. 2, *10*).

As a source of energy we use compressed air at a pressure of 1,500 lb. per square inch, contained within an ordinary commercial metallic container (Fig. 3, *29*). This container is connected with a demand regulator (Fig. 3, *25*), which in turn is connected to a low-pressure tank (Fig. 3, *23*). This low-pressure tank is connected by means of metallic tubing (Fig. 3, *17*) to the hollow cylinder containining the piston (Fig. 3, *12*). There are two valves controlling the inflow and outflow of air to the cylinder (Fig. 3, *13*, *16*). There are two manometers in connection with the regulator (Fig. 3, *24*, *26*), one to register the pressure in the high-pressure container, the other to register the low-pressure system which may be regulated from 0 to 100 lb. per square inch. A third manometer (Fig. 3, *21*) which also registers pounds per square inch in the low-pressure system is so placed in the finished machine that its dial can be easily read. (Two low-pressure manometers are not really necessary but we use them to check one against the other). The radiopaque substance will actually be injected at a pressure four times greater than the air pressure registered on the low-pressure manometers, since the cross-section area of the piston (Fig. 2, *22*) is four times greater than that of the plunger (Fig. 2, *9*). Constant injecting pressure in the low-pressure system is maintained by the high-pressure reservoir (Fig. 3, *29*) through the regulator (Fig. 3, *25*).

The machine is provided with an ordinary tire valve (Fig. 3, *18*), through which air can be pumped by hand or by a mechanical compressor, against the possibility that commercial compressed air may not be available.

All the described parts of the machine are contained within a steel case 18 in. × 18 in. × 30 in., provided with rubber wheels and lock doors (Fig. 4). The machine weighs 78 kilograms.

Operation: The syringe and the vinyl tube are placed in a germicide solution (we use methyldodecylbenzyl trimethyl ammonium chloride solution).* Once the connecting system is placed in proper relation to the "organ-host", the

*Obtainable from Clay Adams Co. Inc., New York, under the trade name "C.R.I."

syringe is throughly washed with sterile saline solution at 40° C. and placed in position in the steel frame, as shown in Fig. 5.

The vinyl tube is now attached to the tip of the syringe, and the stopcock releasing the opaque substance into the vinyl tube is opened. The free end of the vinyl tube is immersed into a sterile graduated glass cup containing the radiopaque substance previously heated to 40° C. The exhaust valve is opened; this causes the piston and plunger to go down slowly and suction the radiopaque substance into the syringe. A few more cubic centimeters than those planned to be injected should be admitted into the syringe. The exhaust valve is now closed and the air of the commercial compressed air container is admitted into the low-pressure system at a pressure not higher than 10 lb. per square inch.

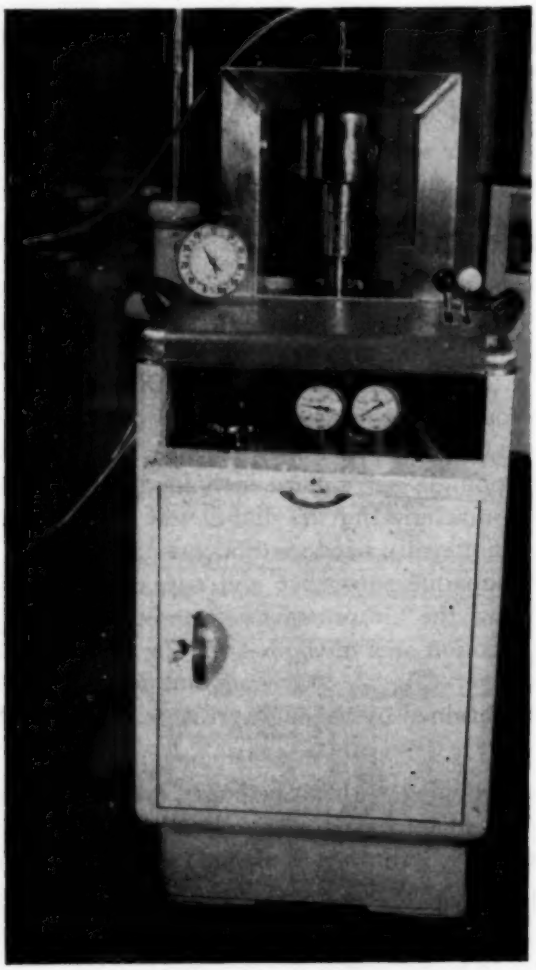

Fig. 4.—Complete machine.

The inflow valve (Fig. 3, *13*) is now opened, thus causing the piston and plunger to move upward slowly. The air overlying the column of radiopaque substance is thus expelled and when nothing but radiopaque substance flows through the transparent vinyl tube, the stopcock is closed. The ring controlling the micro-

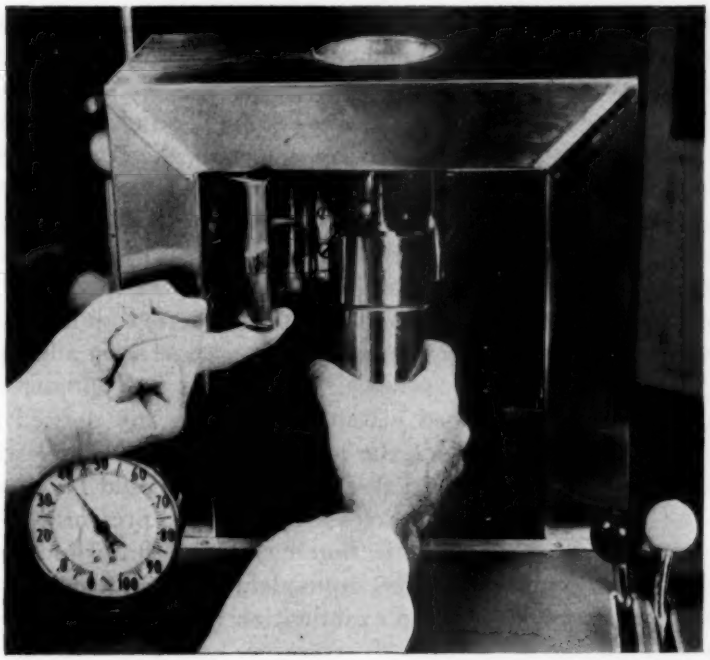

Fig. 5.—Placing syringe into breech. Black knob is inflow valve; white knob, exhaust valve. Low pressure manometer indicates actual injecting air pressure.

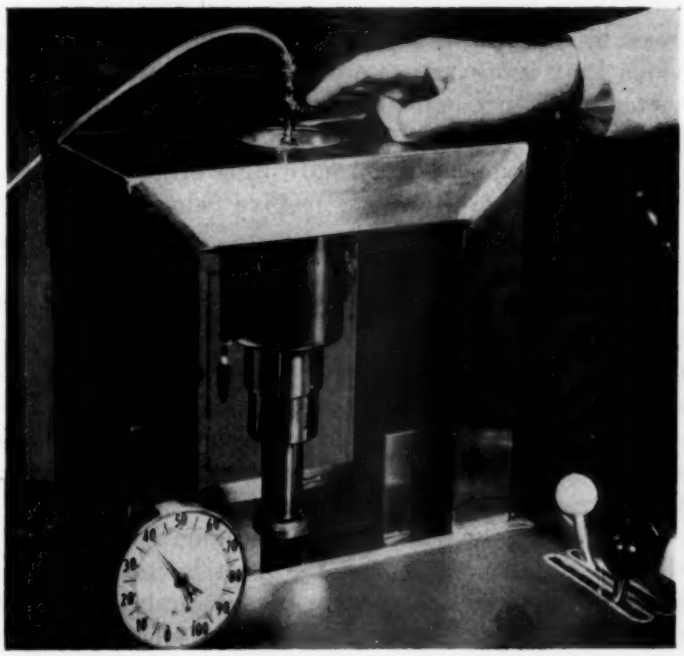

Fig. 6.—Finger ready to open stopcock which will initiate fully automatic injection, cassette changing, and x-ray exposures.

switch is placed in a position such that the seriograph and the x-ray machine will be started exactly at the desired moment during the injection. Previous experience and the careful evaluation of the patient under study are important in selecting the timing of the microswitch. The free end of the vinyl tube is now attached to the connecting system and by means of the regulator (Fig. 3, *25*) the operator can now select the ideal pressure for each connecting system and for the specific anatomic and functional characteristics of a particular "organ-host". Injection should not be started until the operator has assured himself that all members of the team fully realize their duties and that all of the angiocardiographic equipment is ready, since operation from now on is fully automatic. Now the gentle pressure of the finger on the stopcock will start and carry through the rest of the angiocardiographic procedure (Fig. 6).

The injection can be stopped instantaneously at any desired moment by simply closing the stopcock. Once the injection has been completed, the stopcock (Fig. 2, *2*), and the air inlet valve (Fig. 3, *13*) should be closed, and the exhaust valve (Fig. 3, *16*) opened to release the trapped pressure.

The apparent high pressure of injection may appear hazardous (up to 100 lb. per square inch in the lower cylinder, equivalent to 400 lb. per square inch in the interior of the syringe) but the examination of simple physical principles, involved in determination of pressure, velocity, and flow, will show that the pressures obtained with our machine are the necessary ones for modern angiocardiographic techniques and that no added risks are involved.

The application of Poiseuille's law to the study of our connecting systems shows that $P_1 - P_2 = F\,R$, where P_1 is pressure at the proximal end of the catheter and P_2 at the distal end (in this case P_2 may be very small or even equal to zero), F is flow (volume injected per unit of time or output) and R is flow resistance.

It is obvious that using the same connecting system (same length and caliber of catheter) resistance is maintained constant and that if in this system we want to increase flow, we have to increase pressure. The high pressure in the proximal end of the connecting system will be utilized in order to overcome the high resistance of the catheter and to give velocity to the injected fluid. This velocity can be easily calculated according to the formula $V = \frac{F}{q}$, where V is velocity, F is flow and q is the cross-section area of the catheter. Consequently, with a narrow connecting system the velocity will be very high and the narrower the bore the greater the velocity will be if the same rate of flow is to be maintained.

Jönsson and associates[16] were aware of this problem when they advised against the use of cardiac catheters of bore 8F or less when the "organ host" was the right ventricle, because of the danger of provoking extrasystoles or more serious arrhythmias through mechanical stimulation of the interventricular septum by the jet of radiopaque substance.* It is clear then that at the tip of the connecting system which lies within the "organ-host", the problem is not the pressure of the injected fluid but the velocity of the stream head. This velocity is, fortunately, damped by the blood contained within the "organ-host".

*In this institute, Rodriguez and Sodi-Pallares[10] have elicited in dogs ventricular extrasystoles by stimulating the interventricular septum with a jet of physiologic saline solution.

Another untoward effect of the velocity of the jet at the tip of the catheter is that the higher the velocity the greater the recession of the catheter, thus displacing its tip during injection from the site where it was placed by the operator. However, this can be eliminated by using wider catheters (9F, 10F) or, as has been proposed recently by Nordenström,[41] by placing two openings immediately before the previously occluded tip, so that the jets will cancel each other. Multiple lateral perforations at the distal end of the catheter and occlusion of the tip bore have been suggested by one of us (R-A.) and experimentally gave good results. These perforations give shower-like jets, and the increased cross-sectional area of the perforations diminishes the velocity of the streams. Also, by opposition, the jets cancel each other. This will also avoid the possible creation of streamline flow of the radiopaque substance.

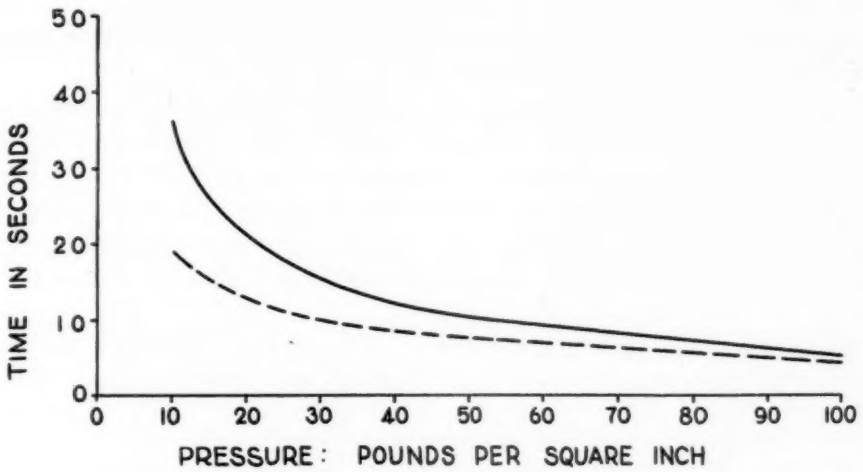

Fig. 7.—Graph correlating time and pressures necessary to inject 50 c.c. of 70 per cent Diodrast (solid line) and tap water (broken line) through an 8F, 100 cm. length Cournand type cardiac catheter, against atmospheric pressure.

Furthermore, closer analysis of the actual events occurring within the "organ-host" at the time of injection reveals that using high-resistance connecting systems it is nearly impossible to distend the "organ-host" to a dangerous degree; the injected amount of radiopaque substance flowing through the catheters is always small (i.e., with the use of Cournand catheters 8F and 9F Jönsson and associates[38] have injected 50 c.c. in approximately 5 and 2 seconds, respectively, and we have found this to be true in a number of cases of thoracic aortography). Therefore, dangerous distention or overfilling of the "organ-host" are easily avoided with the high-pressure machine. The pressure within the "organ-host" will only become hazardous when the volume of opaque substance injected is great and out of proportion to the outflow from the "organ-host."[34,42] Tables have been constructed for different connecting systems which show the relationship between radiopaque substance outflow and the pressure required. One such table is presented in Fig. 7 as an illustration.*

*We have found in vitro and experimentally in dogs that with the high pressures obtained by our machine the pressure within the organ-host has no influence on the outflow of radiopaque substance.

We have used this injecting machine, which we have called "Presoyector", for aortographies, selective angiocardiographies, arteriographies, and venographies with excellent results.

We believe that it meets the needs of modern angiocardiography and can even contribute to other fields, such as the determination of circulation time, by coupling fluorodensographic equipment to it and making selective fluordensography possible,[41,43,49] as well as in cineangiography, etc.

SUMMARY

Some of the technical drawbacks involved in the injection of radiopaque substances through different connecting systems for angiocardiography are discussed.

The different techniques and apparatus used for injection as well as their physical principles are briefly analyzed together with some of the hemodynamic variables obtained in different "organ-hosts".

If good angiocardiographic plates are to be obtained with present-date cardiac catheters high-injecting pressures must be used in order to obtain the optimal flow rates of radiopaque substances.

A machine was devised and constructed to fulfill this basic requirement with a maximum of safety, with optimal injecting pressures which produce high-contrast plates, and with fully automatic synchronization of injection, x-ray exposure, and cassette changing.

The machine may find application in other fields. When all the pitfalls of cineangiography are surpassed this machine will solve the basic problem: injection.

SUMMARIO IN INTERLINGUA

Es discutite alicunes del disavantages involvite in le injection de substantias radio-opac, que es requirite pro fines angiocardiographic, via le diverse "systemas connective" (i.e. le agulia, tubo, o vasculo sanguinee que le injicite substantia traversa inter le mechanismo injectori e le segmento cardiovascular sub investigation). Le technicas e apparaturas nunc in uso e le applicabile principios physic es brevemente analysate. Etiam le variabiles hemodynamic obtenite per injicer le substantias radio-opac a in varie organos es discutite.

Le catheteres cardiac nunc disponibile require alte pressiones injectional pro que le fluxo del substantias injicite permitte le production de bon angiocardiogrammas. Nos ha construite un injector que corresponde a iste requirimento. Simultaneemente illo functiona con un minimo de risco e es characterisate per su synchronisation completemente automatic de injection, radioexposition, e cambiamento del cassetta. Le nove injector es describite in detalio. Su possibile usos in altere campos es mentionate.

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Clinical Reports

ACUTE BACTERIAL ENDOCARDITIS FOLLOWING MITRAL VALVULOPLASTY

NORMAN PANTING, M.D.,* MARVIN A. EPSTEIN, M.D.,** AND ALFRED A. BOLOMEY, M.D.***

OAKLAND, CALIF.

AN extensive review of the literature[1-5] has failed to reveal any cases of mitral stenosis in which bacterial endocarditis developed shortly after valvuloplasty. The occurrence of bacterial endocarditis in this patient is reported in the hope that it will focus attention on this possibility as a complication of mitral valve surgery and thus increase the alertness of physicians engaged in the surgical relief of mitral stenosis. It is of further interest to note that despite the grave outlook held for patients with staphylococcal endocarditis[6,7] the disease was arrested in this patient and that now, two years after surgery, she remains clinically well.

CASE REPORT

The patient was a 35-year-old white married female, admitted to the Kaiser Foundation Hospital on March 2, 1952, for mitral valvuloplasty.

At the age of 15 she had acute rheumatic fever and eleven years later, on a routine physical examination, a cardiac murmur was first noted. Since then she had noted a slowly increasing exertional dyspnea and transitory palpitation. At the age of 31, following a sore throat, the patient was ill with recurrent acute rheumatic fever symptoms lasting 2 weeks.

In 1949, at the age of 33, during a routine examination the diagnosis of rheumatic heart disease with mitral stenosis was established. Because of recurrent attacks of tonsillitis, tonsillectomy and adenoidectomy were advised and performed. On Feb. 3, 1952, the patient had an episode of paroxysmal auricular fibrillation. Regular sinus rhythm returned after receiving lanatoside C and quinidine sulfate, and she was discharged on a maintenance dose of quinidine.

Physical findings: On admission for surgery, her temperature was 98.7° F.; blood pressure, 130/80 mm. Hg; pulse regular at 76/min. The heart was not enlarged to percussion, but there was a prominent apical impulse. Auscultation revealed a Grade 3 rumbling mitral diastolic murmur with presystolic accentuation. M_1 and P_2 were accentuated. One examiner noted a faint aortic systolic murmur. The laboratory data were as follows: hemoglobin 12.1 grams;

From the Department of Medicine, Cardiac Service, Kaiser Foundation Hospital, Oakland, Calif.
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*Now First Lieutenant, U. S. Air Force (MC) Edwards Air Force Base, Calif.
**Formerly Visiting Physician in Internal Medicine, Highland-Alameda County Hospital, Oakland, Calif.; Now Captain, U. S. Army (MC), Army Chemical Center, Md.
***Chief, Cardiovascular Clinic, Kaiser Foundation Hospital, Oakland, Calif.

white blood count, 8,700; differential, normal. Sedimentation rate, 14 mm. per hour (Westergren); urinalysis, negative; serology, negative. A chest x-ray showed a moderate left auricular enlargement consistent with mitral stenosis. An electrocardiogram showed a regular sinus rhythm and S-T and T changes consistent with digitalis and quinidine effect.

The patient was given penicillin 300,000 units every six hours and streptomycin 1 Gm. daily prophylactically, in addition to maintenance doses of digitalis and quinidine. On March 4, 1952, a mitral finger-fracture valvuloplasty was done, using the procedure recommended by Harken and associates.[1] Surgery lasted 3½ hours and was well tolerated despite paroxysmal ventricular tachycardia and paroxysmal auricular fibrillation during the operation, which were controlled by 0.2 per cent procaine amide, intravenously. The mitral valve barely admitted the tip of the surgeon's finger at the start of surgery and had an orifice of about 1.5 cm. at the conclusion of the procedure.

Postoperatively, streptomycin, 0.5 Gm. every six hours, was given and penicillin was continued. On the tenth postoperative day, when she seemed to be doing well, the patient developed a severe sore throat, postnasal drip, chills, and fever of 103° F. An otolaryngologist found only a catarrhal rhinitis and a purulent postnasal discharge with no evidence of sinusitis. X-rays of the sinuses and chest were negative. A careful general physical examination revealed no new findings. A white blood count was 7,600 with a differential of 71 per cent polymorphonuclears, 8 per cent lymphocytes, and 4 per cent monocytes. A blood culture was taken.

Because of these findings, oxytetracycline 0.5 Gm. every six hours was started, and during the next 3 days the patient felt much better except for moderate nausea from the drug. The sore throat disappeared completely, and there was a marked decrease in the postnasal discharge. She continued, however, to run a spiking fever of 101 to 102.5° F. On March 17, she developed chills, a fever of 105° F. and experienced marked general malaise, anorexia, and headache. Her white blood count was 7,700 and a cleanly voided urine sediment showed 15 to 20 red blood cells and 8 to 10 white blood cells per high-power field. No bacteria were seen. On the same date, the laboratory also reported that a coagulase-positive hemolytic *staphylococcus aureus* was growing in the initial blood culture of March 14. Blood cultures taken on March 16, 17, and 18 also grew the same organism.

Because of this clinical picture and the positive blood culture, a diagnosis of acute bacterial endocarditis was made. Penicillin was, therefore, increased to 1.5 million units every three hours intramuscularly and oxytetracycline increased to 0.5 Gm. every four hours, intravenously. On March 18, her temperature came down from 103.4° to 100°F. Oxytetracycline, chlortetracycline, and streptomycin were discontinued on that date when sensitivity studies on the isolated organism showed it to be resistant to them as well as to penicillin, to chloramphenicol in 2 milliequivalent concentrations, and to 2 units of bacitracin. The staphylococcus was highly sensitive to chloramphenicol in 20 milliequivalent concentrations, to sulfisoxazole (Gantrisin), and to 20 units of bacitracin. Therefore, chloramphenicol 3 Gm. daily and sulfisoxazole 10 Gm. per day were started orally.

On March 19, for the first time, a definite to-and-fro friction rub was heard over the entire precordium. This gradually diminished in intensity over the next two days. The previous diastolic rumble was thought to be considerably louder, but careful scrutiny failed to reveal petechiae, splinter hemorrhages, or splenomegaly. Penicillin was increased to 50 million units per day, intravenously. Because of anorexia, nausea, and vomiting, nutrition was maintained with intravenous fluids. Probenecid (Benemide) was begun but could not be continued because of intolerance. On the morning of March 19, a sinus tachycardia of 120 and bilateral basilar rales were noted, and additional digitalis was given. The same evening auricular fibrillation appeared, and she was given more digitalis. Under this regimen her clinical picture improved considerably and she became afebrile.

On March 25, a temperature rise to 100.8° F. was noted and after this penicillin was administered intravenously as a continuous slow drip, 60 million units daily. Sulfisoxazole was also increased to 15 Gm. per day. Three blood cultures were negative, however. The patient continued to improve, tolerating diet and oral medications well, although she was still fibrillating slowly. On March 28, because of low-grade fever, the penicillin dosage was again increased, this time to 90 million units daily. She became afebrile on March 30.

On April 2, a new diastolic murmur was noted over the left sternal border in the second intercostal space, becoming louder two days later. This was thought to be either aortic or pulmonic in origin. On April 6, the patient began to run a low-grade fever, and she developed a tachycardia. On April 13, since these signs persisted, penicillin was discontinued to observe any modification in her course. The next day the patient became afebrile. The left sternal basal diastolic murmur remained unchanged, but the friction rub was only faintly heard. On April 17, as a precautionary measure, chloramphenicol was increased to 4 Gm. per day and sulfisoxazole to 20 Gm. per day. The patient remained on these dosages until April 30 when sulfisoxazole was discontinued, and on May 5 chloramphenicol was stopped. Chest x-ray taken on May 3 revealed hilar and pulmonary congestion bilaterally and comparison with a previous film of March 16 revealed a slight increase in transverse cardiac diameter.

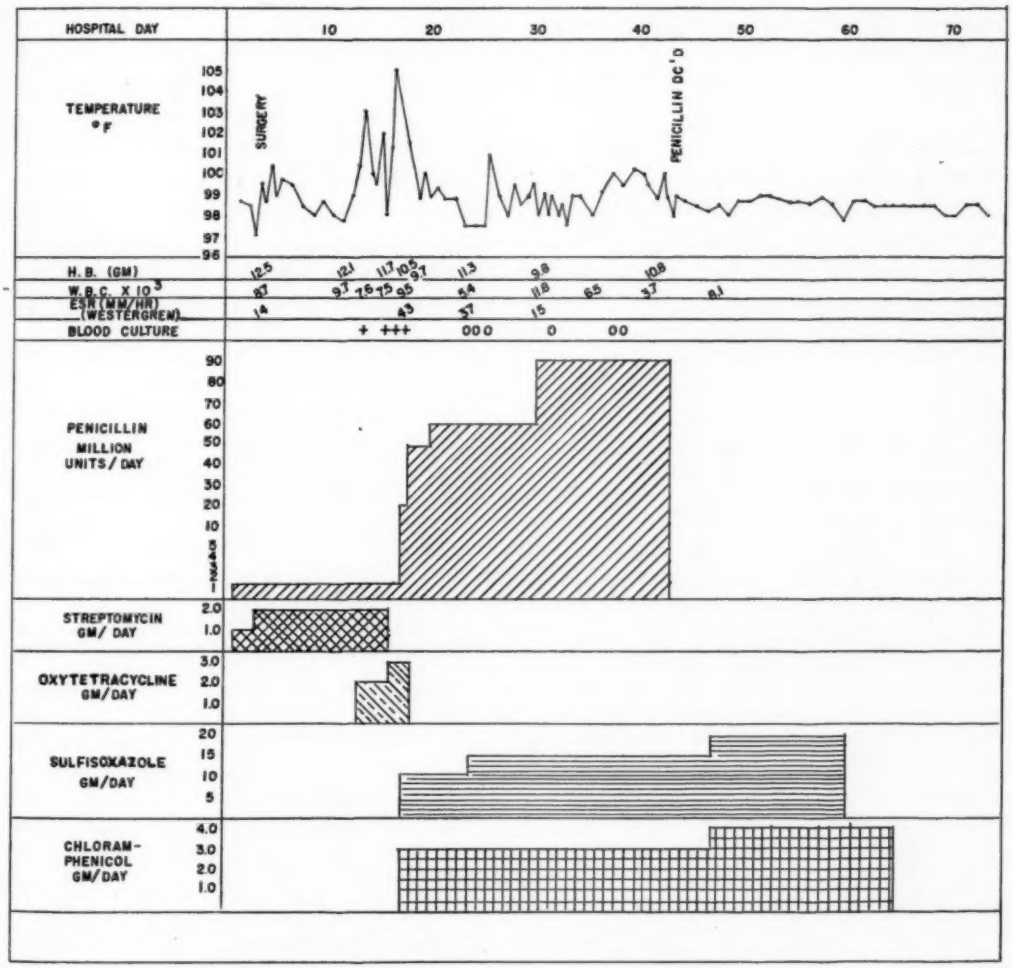

Fig. 1.—Clinical course of patient with acute bacterial endocarditis.

The patient was sent home on May 13, 1952, completely afebrile, fibrillating slowly, with maintenance digitalis as her only medication. During her hospitalization, she had received 1,545,000,000 units of penicillin in 41 days; 163.5 Gm. of chloramphenicol in 49 days; 547.5 Gm. of sulfisoxazole in 44 days; 17.5 Gm. of streptomycin in 13 days; 8.5 Gm. of Terramycin in 5 days.

The patient returned for conversion of her auricular fibrillation in June, 1952. This was accomplished with quinidine, and maintenance doses were prescribed. Three consecutive blood cultures were negative at this time. Comparison of chest x-ray with previous films revealed reduction in transverse cardiac diameter as well as in hilar markings.

Over the last 2 years the patient has remained essentially unchanged in serial follow-up study.

SUMMARY

This report is believed to be the first published case of acute staphylococcal endocarditis as a complication of surgery for mitral stenosis. Apparent cure followed the administration of huge doses of penicillin, sulfisoxazole, and chloramphenicol over a period of 44 days. Two years after the discontinuance of therapy the patient remains apparently cured.

SUMMARIO IN INTERLINGUA

Es reportate un caso de acute endocarditis staphylococcal occurrente como complication in consequentia de un intervention chirurgic pro stenosis mitral. Un extense revista del litteratura ha convincite le autores que isto es le prime publication de un tal reporto. Le administration de enorme doses de penicillina, sulfisoxazol, e chloramphenicol durante un periodo de 44 dies resultava in un cura apparentemente complete. Al presente tempore, i.e. duo annos post le discontinuation del therapia, le stato curate del patiente persiste sin cambiamento.

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BULLET WOUND OF THE LEFT VENTRICLE

THOMAS W. INMON, LIEUTENANT COLONEL, MC, USA, AND
B. E. POLLOCK, COLONEL, MC, USA

SAN FRANCISCO, CALIF.

RECENTLY an opportunity to study a patient who sustained a bullet wound of the lateral aspect of the left ventricle was presented to us. Surgical exploration and repair of this wound were performed, and serial electrocardiograms were recorded. This combination of factors provided an opportunity to correlate the electrocardiographic findings with a myocardial lesion of known location in a living patient rather than retrospectively on the basis of postmortem findings.

CASE REPORT

A 28-year-old Negro soldier sustained a gunshot (carbine) wound of the chest on December 16, 1953. He was admitted to Letterman Army Hospital and taken directly to the operating room. Examination revealed the wound of entrance to be located in the fourth left intercostal space about 4 cm. lateral to the edge of the sternum. The wound of exit was found in the left eighth intercostal space posteriorly 7 cm. from the spine. The patient was conscious but in mild shock; blood pressure was 80/40 mm. Hg. Breath sounds were normal in both lung fields. There was no evidence of abdominal injury, and the general condition of the patient appeared to be satisfactory for immediate surgical intervention. A blood transfusion was begun, anesthesia administered, and the chest was entered through an incision in the fourth left intercostal space. The heart was visualized, and it was seen that the course of the bullet had been tangentially through the outer wall of the left ventricle just lateral to the anterior descending branch of the left coronary artery. The cavity of the left ventricle had not been entered. The wound in the myocardium was circular, approximately 4 cm. in diameter, and involved most of the thickness of the wall of the left ventricle (Fig. 1). The surgeon had the impression that the heart might rupture through this myocardial wound at any moment, but no systolic pulsations were noted. Since the size of the wound precluded closure by suture, a free pericardial graft just larger than the size of the wound was sutured into place over the defect. The parietal pericardium was then closed loosely. Wounds in the left lung were then closed, a soft rubber catheter was placed in the chest through the sixth intercostal space in the midaxillary line, and the primary incision was closed in layers. The patient withstood the operative procedure well, and at the termination the blood pressure was 140/75 mm. Hg.

During the postoperative course, a circumscribed area of radiolucency with rather thick walls developed in the left lung along the left border of the cardiac silhouette as visualized in the posteroanterior roentgenograms of the chest (Fig. 2*A*). This lesion was localized posteriorly in the lateral view. It was considered to represent a localized lung abscess in the wound tract. On December 18, the patient's temperature was 100.5° F. He had low-grade fever until January 4, 1954, and was afebrile thereafter. He was given antibiotics and pleural drainage was continued.

From the Cardiology Service, Letterman Army Hospital, San Francisco, Calif.
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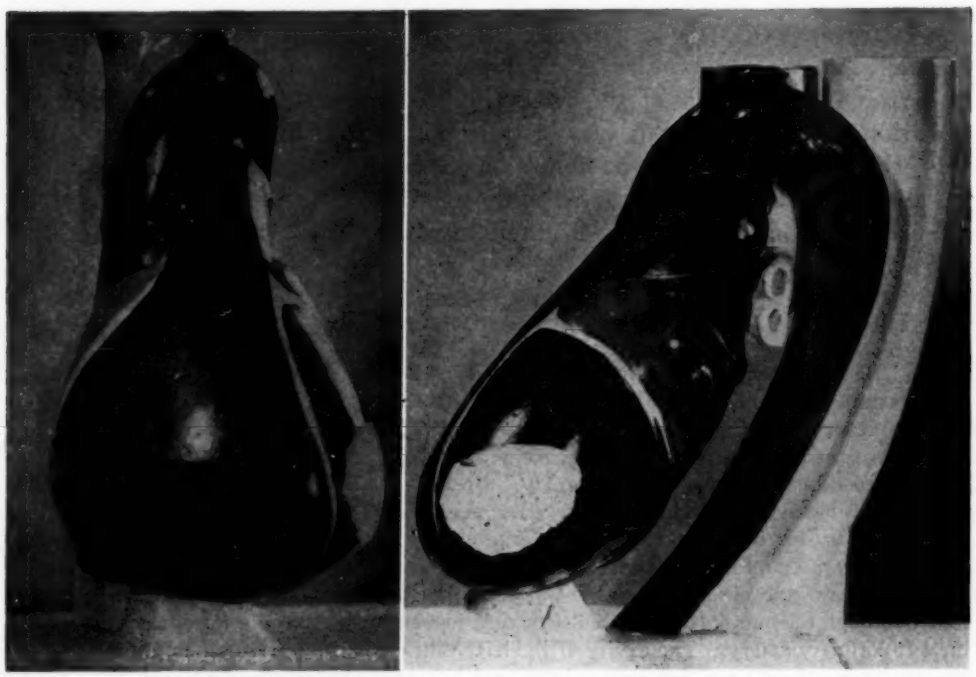
Serial roentgenograms demonstrated a gradual clearing of the lung abscess (Fig. 2 *B*). On January 25, antibiotic medication was discontinued with no recurrence of symptoms or signs of infection.

Serial electrocardiograms were taken throughout the hospital course. The first, on the morning following injury, was abnormal with changes of the type usually seen in acute lateral wall myocardial infarction (Fig. 3). By December 18, the presence of a pericardial friction rub and changes in the electrocardiogram indicated the presence of a superimposed pericarditis (Fig. 4). Further serial electrocardiograms demonstrated changes consistent with the usual involution of both processes (Fig. 5).



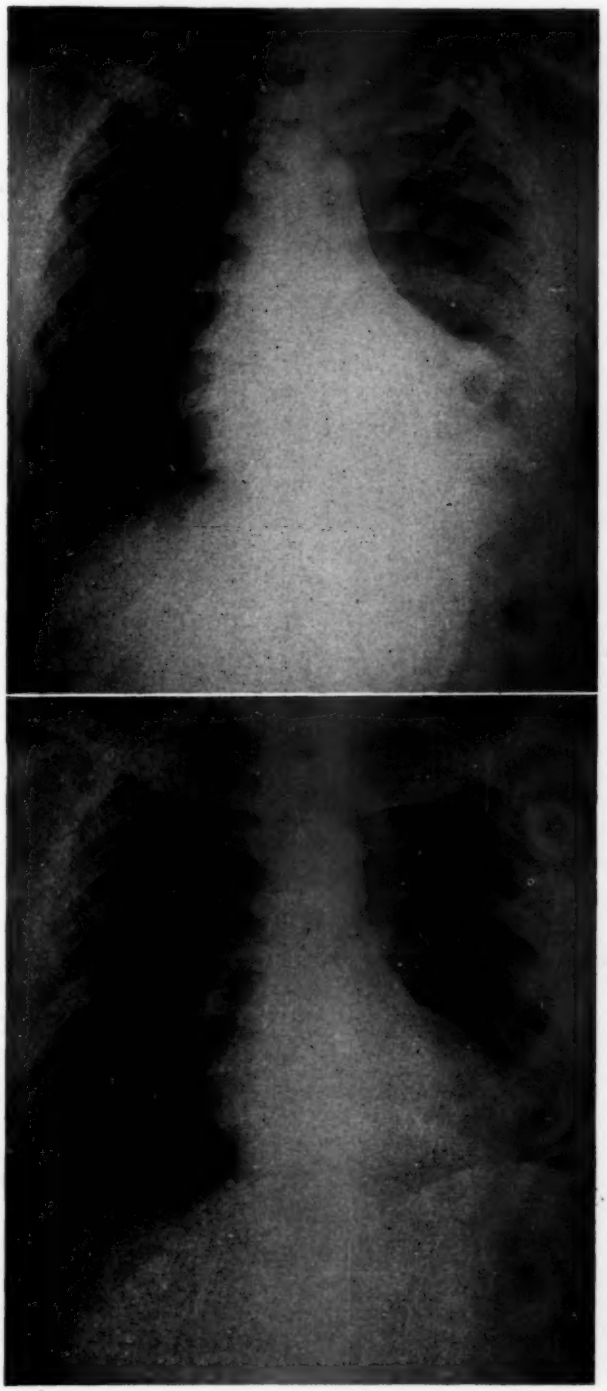
A. *B.*

Fig. 1.—Location of cardiac wound demonstrated by white patch on plaster model of heart. *A*, Frontal view. *B*, Left lateral view.

The leukocyte count on December 18 was 22,200 per cubic millimeter with a differential cell count of 84 neutrophils, 11 lymphocytes, and 5 monocytes. By January 11, the leukocyte count had returned to normal levels. Following healing of the pulmonary abscess, the patient was ambulated and given physiotherapy to the shoulder girdle. He made a complete clinical recovery and was able to engage in ward activities. Cardiac fluoroscopy, performed on Feb. 12, 1954, revealed the presence of normal cardiac activity without paradoxical pulsation in any area. Pleuropericardial adhesions were demonstrable along the border of the left ventricle.

During the course of convalescence, the patient's behavior was schizoid. After psychiatric study he was discharged from the Army and left the hospital.

A.



B.

Fig. 2.—Roentgenograms of the chest showing *A*, lung abscess in left lower lobe, and *B*, residual fibrosis after healing of the lung abscess.

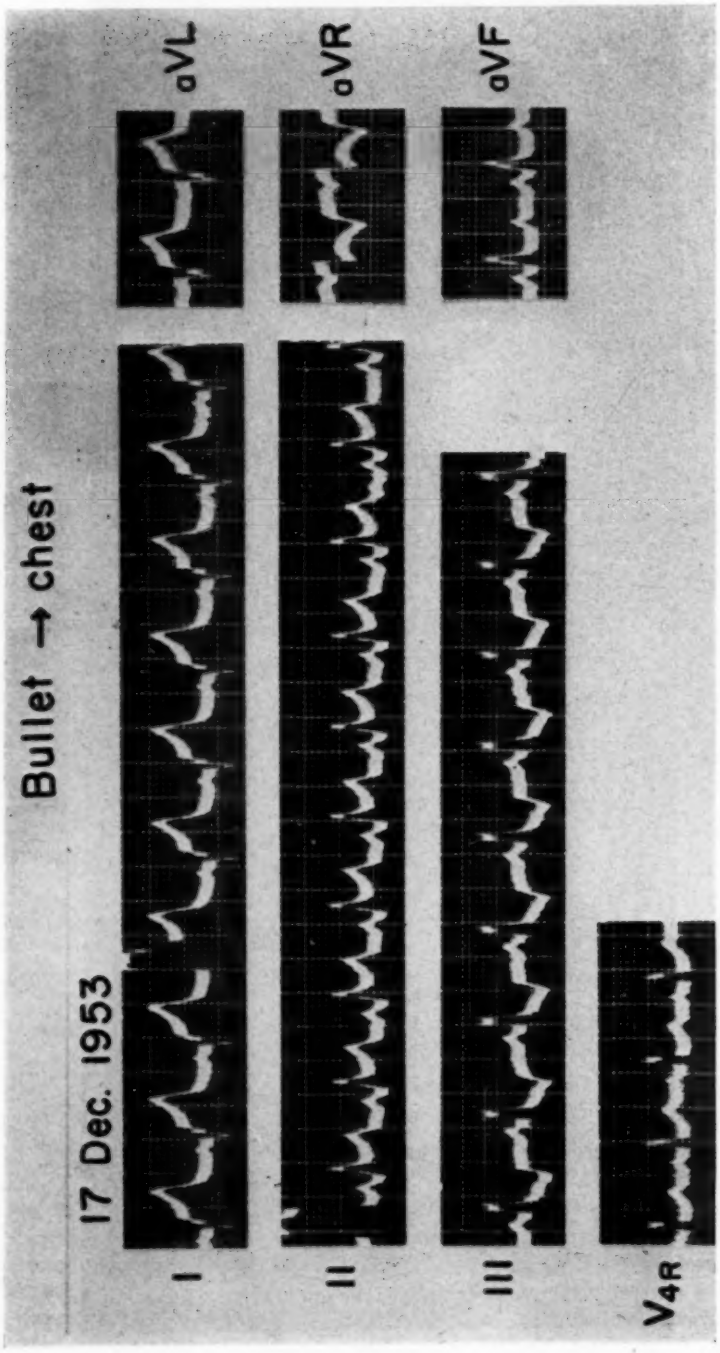


Fig. 3.—Initial electrocardiogram. The findings in Leads I and aV_F are consistent with recent lateral wall myocardial infarction.

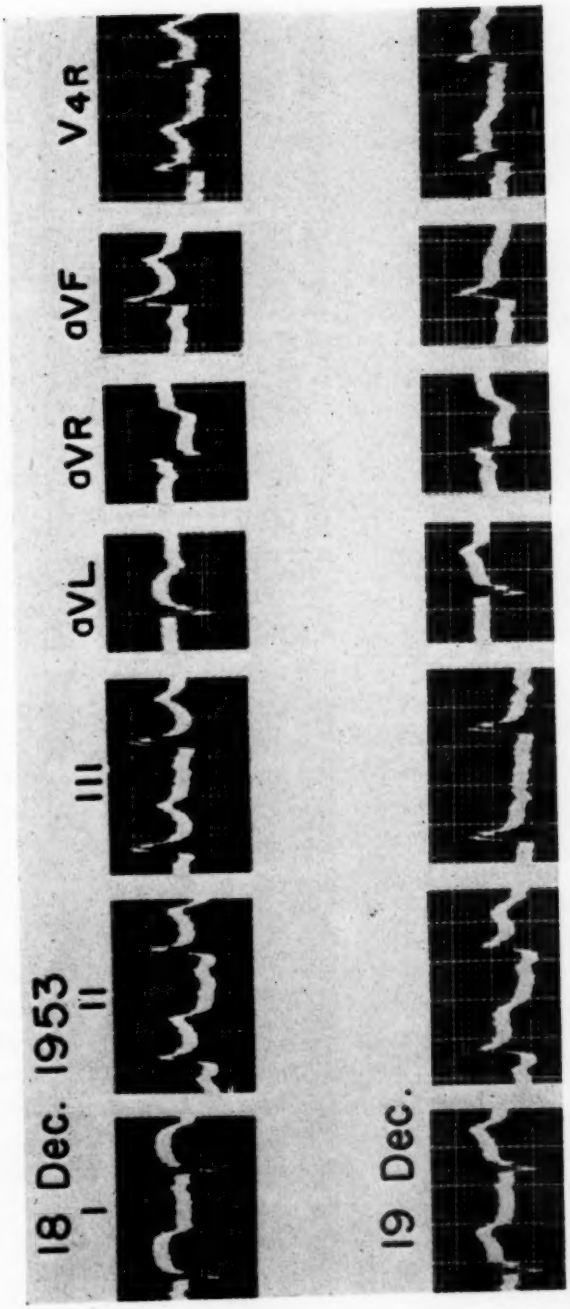


Fig. 4.—Follow-up electrocardiograms. A pericardial friction rub was present at this time.

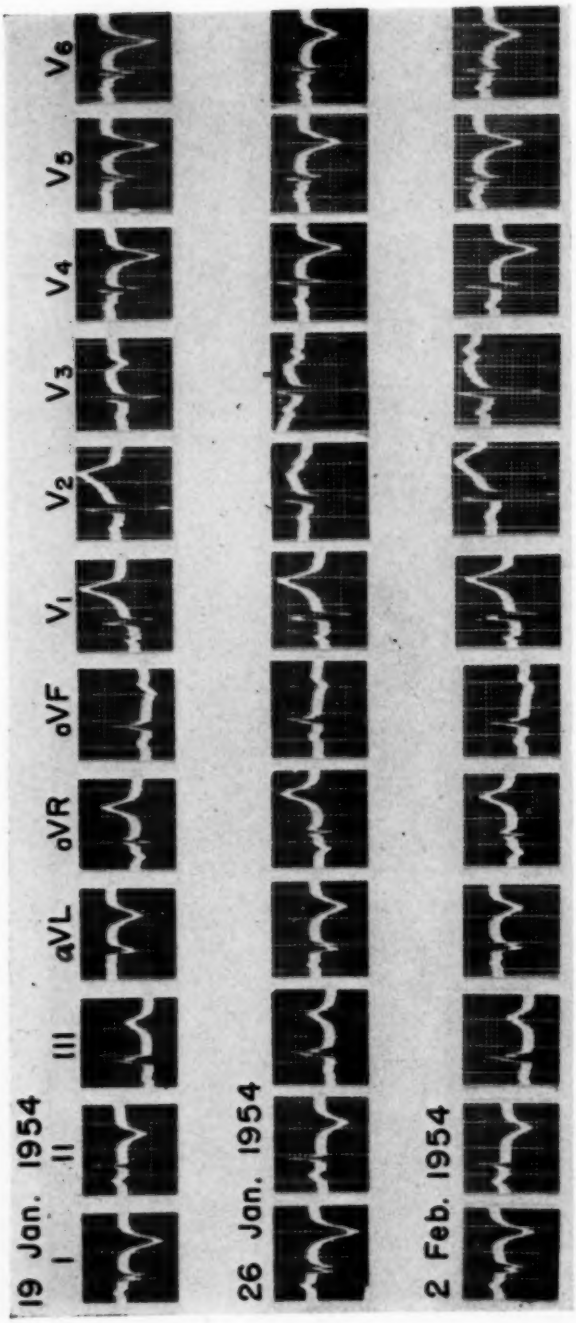


Fig. 5.—Later electrocardiograms showing minor changes consistent with healing.

DISCUSSION

The opportunity to observe an extensive myocardial injury by direct inspection and thereafter to follow the course with serial electrocardiograms must be very infrequent. A study of the literature has failed to reveal a report of a similar case, although many instances of puncture, incision, laceration, and contusion injury of the heart are reported.[1,2]

In this patient the location of the myocardial lesion was demonstrated surgically (Fig. 1). Subsequent electrocardiograms (Figs. 3, 4, 5), reveal evidence which we consider consistent with damage to the anterolateral aspect of the myocardium. This interpretation correlates with the facts demonstrated at surgery. The findings in Lead aV_L are of particular interest and indicate the value of this lead in lateral wall-infarction localization.

Prinzmetal, Kennamer, Shaw, and their associates[3-6] believe that the epicardial 20 per cent of the myocardial thickness constitutes the principal portion of the ventricular myocardium contributing to R deflections in electrocardiograms taken over the intact myocardium. They have shown in experiments on normal dog hearts that when the tip of a needle electrode is at the center of the ventricular myocardial thickness, a QS deflection is inscribed on the electrocardiogram; placement of this electrode within the outer (epicardial) portion results in an upright R deflection on the electrocardiogram.[3,4] Along with Bellet and Johnston[7] they have further shown that infarction or cauterization of this superficial layer will result in a QS deflection. Infarction or cauterization not involving the outer 20 per cent of the myocardium produced no appreciable effect on the electrocardiogram recorded from the epicardial surface.[5]

The electrocardiographic data in our case tend to support the observations briefly cited previously, particularly in Leads I and aV_L. There are, however, certain factors which render a comparison hazardous. In their experiments on dog hearts from which the superficial 20 to 30 per cent of the ventricular myocardium was removed by a cutting cautery, Prinzmetal and his associates recorded electrocardiograms directly over and within the myocardial wall and within the cavity as well. No such records were taken on our patient. Perhaps more important is the fact that the ventricular myocardium in our patient was damaged by a high velocity missile. It is well established that injuries to muscle produced by such missiles are far more widespread in their pathologic and physiologic effects than is apparent on gross examination. From this standpoint, it appears likely that our patient had a temporary transmural injury. It is unfortunate that exploratory chest leads could not have been taken during the early period of his hospitalization.

SUMMARY

The case is presented of a patient who sustained a gunshot wound of the left ventricle which was visualized at surgery. Serial electrocardiograms were taken. Such a case provides a rare opportunity for correlating the anatomic and electrocardiographic location of myocardial lesions in the living human being. In this case the localization possible from electrocardiographic study was well correlated with the known location of the lesion.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un patiente in qui le ventriculo sinistre habeva essite ledite per un colpo de fusil e in qui le lesion deveniva accessibile a directe examination visual durante le intervention chirurgic. Electrocardiogrammas esseva facite in serie. Un tal caso offere le rar opportunitate de studiar le correlation del sito anatomic con le sito electrocardiographic de un lesion myocardial in un vive patiente human. Il esseva constatate que le localisation del lesion per medio del studio electrocardiographic coincideva ben con le location del lesion cognoscite per observation directe.

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TRICUSPID STENOSIS AND CONSTRICTIVE PERICARDITIS IN ONE PATIENT SUCCESSFULLY TREATED BY SIMULTANEOUS VALVULOTOMY AND PERICARDECTOMY

HANS KROOK, M.D., GUNNAR BIÖRCK, M.D., AND HELGE B. WULFF, M.D.

MALMÖ, SWEDEN

CLINICALLY significant tricuspid stenosis is rare, and usually occurs in combination with other valvular lesions, mostly affecting the mitral valve. This other valve lesion then, generally, is the more important, and the clinical diagnosis of tricuspid stenosis may be overlooked.

O'Neil and associates[4] have recently reported from the literature on the incidence of tricuspid valvular lesions in 806 cases of chronic rheumatic valve disease. A figure of 30 per cent for tricuspid valve involvement is given, though all these lesions appeared in combination with other valvular lesions. This figure is remarkable. Cooke and White[2] were of the opinion that tricuspid valve lesions, however, in many cases were so slight that they had little clinical significance.

Isolated lesions of the tricuspid valve may be seen in congenital defects like Ebstein's disease or tricuspid stenosis or atresia. Functionally, regurgitation may develop as a result of long-lasting right ventricular failure.[3]

The clinical findings in isolated tricuspid stenosis are: isolated enlargement of the right auricle and symptoms simulating right-sided cardiac failure or constrictive pericarditis, with neck-vein engorgement, enlargement of the liver, jaundice, ascites, peripheral edema, and cyanosis.

Jugular vein tracings, showing prominent *a* and *v* waves, are regarded as diagnostic in a case of sinus rhythm. However, most cases of tricuspid stenosis have auricular fibrillation. If there is a coexisting tricuspid regurgitation, ventricular waves dominate the picture. Cardiac catheterization may, likewise, be of diagnostic value in cases with sinus rhythm if high presystolic waves are recorded in the right auricle.

Since it is obvious that commissurotomy may give equally good results in tricuspid stenosis as in mitral stenosis, making a diagnosis of tricuspid stenosis is now more important than formerly. Trace and associates[1] have recently described one case with combined rheumatic mitral and tricuspid stenosis, treated with first mitral and then tricuspid commissurotomy, and O'Neill and associates[4] have likewise described such a case. In both these patients the tricuspid stenosis was not diagnosed, until the mitral stenosis had been ameliorated by the commissurotomy.

From the Departments of Medicine and Surgery, Allmänna Sjukhuset, Malmö, and the University of Lund, Sweden.

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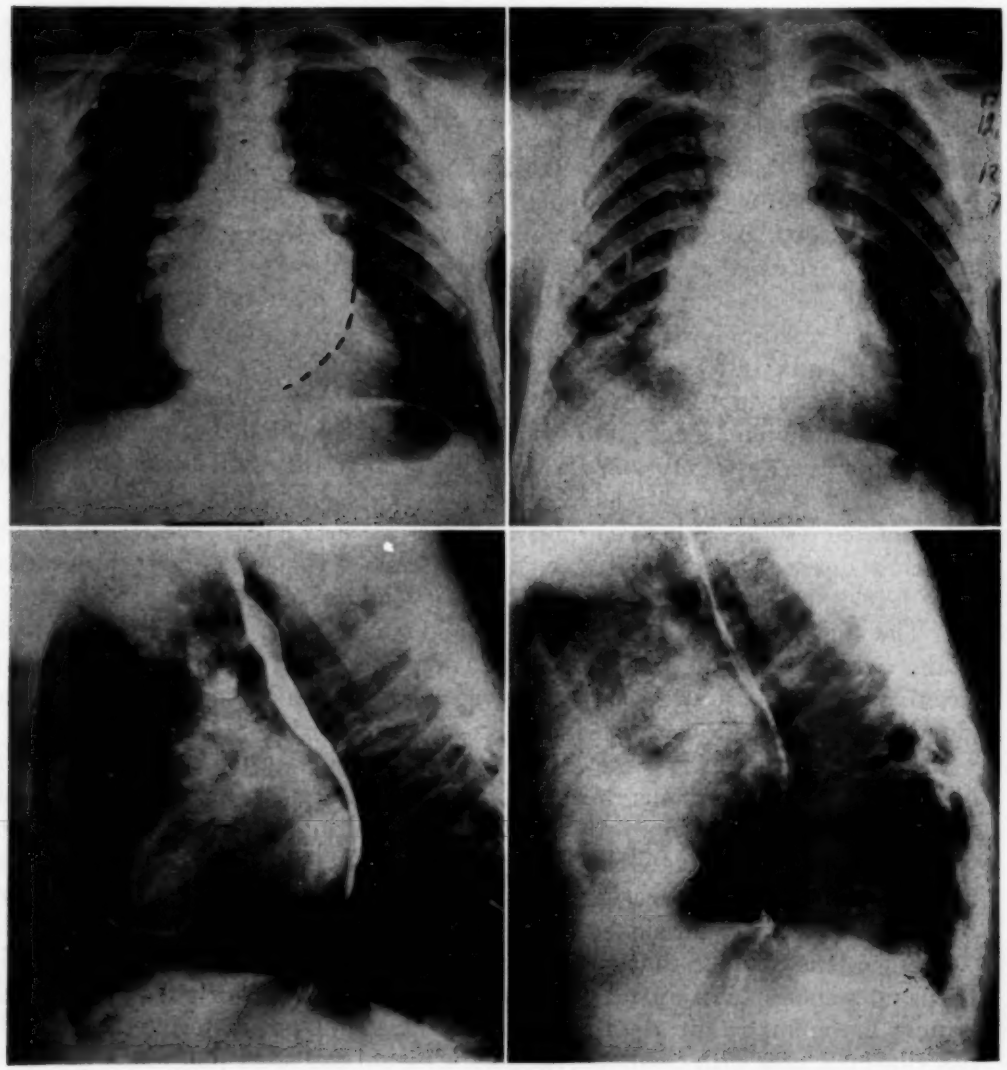
We have recently had occasion to study another patient, who was found to suffer from constrictive pericarditis and in addition, tricuspid stenosis. We have no evidence of any other valvular lesion in this patient. He was operated upon, and during the same operation he was subjected to pericardectomy and tricuspid valvulotomy (finger-fracture). Six months later, he had improved considerably and his venous pressure was normal.



A. *B.*

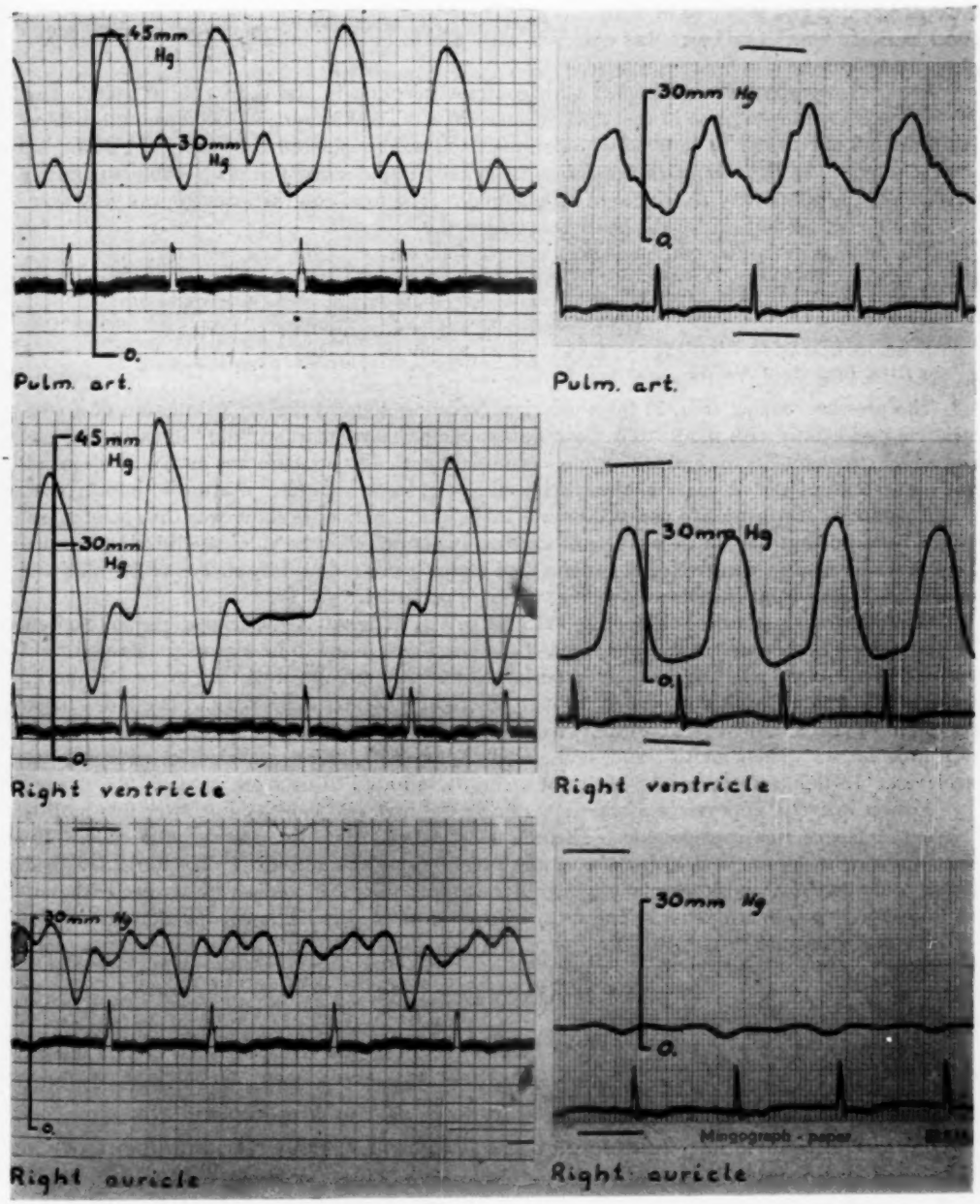
Fig. 1.—*A*, Preoperative; *B*, Postoperative.

CASE REPORT

O.L.H., a 24-year-old man, was never ill until 1950 and did not know of any rheumatic fever. He was employed in heavy work at a farm.

In 1950, he experienced increasing dyspnea at effort, palpitation, and sometimes syncopal episodes at exertion. He consulted a physician in 1952 and, after some rest, continued his work

until January, 1953, when his symptoms got worse and he developed ankle edema, ascites, nytcuria, and a nonproductive cough. He was admitted to the hospital, where these observations were confirmed. In addition, he had cyanosis and auricular fibrillation, but no murmurs and no dyspnea at rest.



A. *B.*

Fig. 2.—*A*, Preoperative; *B*, Postoperative.

He was, then, referred to Malmö Allmänna Sjukhus for further study. These findings were again confirmed. His liver was enlarged and he had ascites. He had auricular fibrillation with a high ventricular rate. No murmur was heard. His second sound was accentuated over the precordium. Blood pressure, 140/85 mm. Hg. The electrocardiogram showed atrial fibrillation, right-axis deviation, normal ventricular complexes. T_I was positive, T_{II} isoelectric, T_{III}, and T_{V4} were negative. On the x-ray (Fig. 1) there was a large, rather massive structure occupying the space behind and to the right of the heart. There was also a crescent-like calcification in the lower pericardium. The heart was enlarged with a calculated volume of 770 c.c. per square meter body surface.

Angiocardiography was performed with contrast injection in the right cubital vein. The contrast was seen to stagnate in the superior vena cava. The afore-mentioned structure behind the heart did not appear to be filled with contrast, and was considered as possibly not belonging to the heart. The right ventricle was of normal size, the pulmonary conus possibly somewhat large, while the pulmonary arteries were rather small. The total contrast passage was very slow, and no filling of the left side of the heart was achieved.

The findings at cardiac catheterization were as follows:

Pressures in mm. Hg

	Rt. aur.	Rt. ventr.		P.A.	
	Mean pressure	Systol.	Diastol.	Mean	"PCV"
Before operation 7/21/53	24	49	23	32	—
After operation 3/4/54	4	32	5	14	8

The pressure tracing (Fig. 2) from the right ventricle showed the typical picture of a constrictive pericarditis with moderately elevated systolic pressure, marked "dip" in early diastole, and a high "plateau" at the end of diastole. The right auricular pressure was markedly elevated, but on account of the fibrillation, the tracing did not give any further diagnostic information.

A diagnosis of constrictive pericarditis was made, and a pericardectomy was thus attempted. It was believed that the nature of the retrocardiac structure might be elucidated during the surgical procedure. Preoperatively, the edema and ascites were reduced by means of digitalis and mercurial diuretics, but the elevated venous pressure persisted.

Operation was performed on Sept. 4, 1953 (H.B.W.). The calcified pericardium was excised. The large structure behind and to the right of the heart was found to be a grossly enlarged right auricle, partly surrounded by a calcified pericardium. After removal of this, access to the interior of the atrium was accomplished through the right auricular appendage. The index finger could barely reach the tricuspid orifice, which was found to be strictured, admitting only the tip of a little finger. The stenosis could, however, be split easily, and a considerable widening was achieved. In this connection, the big right atrium was found to decrease in size.

Postoperatively, improvement was slow during the first two months, but after five months the improvement was considerable. There was no longer cyanosis, edema, or ascites. The liver was almost normal in size, and the venous pressure was again normal. The auricular fibrillation could be converted to regular rhythm by means of quinidine, and a new cardiac catheterization showed no abnormalities. The x-ray showed a marked reduction of the afore-mentioned retrocardiac structure (Fig. 1).

COMMENT

From an etiologic point of view, there is no clue to the origin of either lesion. Microscopic examination of the pericardium did not reveal any specific inflammatory tissue. Were it not for the statement of the surgeon and the apparent effect on right auricular volume of the valvulotomy, the embarrassment of the tricuspid valve would probably have escaped notice. Whether it really was a valvular stenosis proper or rather some kind of stricture caused by the same process that is responsible for the constrictive pericarditis is hard to state. The unsatisfactory filling of a part of the (aneurysmatically dilated?) right auricle at angiocardiography is another unexplained feature of this patient.

SUMMARY

A case of constrictive pericarditis combined with stenosis of the tricuspid valve is reported. Simultaneous pericardectomy and tricuspid valvulotomy were performed with a good result.

SUMMARIO IN INTERLINGUA

Es reportate un caso de constrictive pericarditis in combination con stenosis del valvula tricuspide. Si o non le duo lesiones esseva connectite in lor etiologia non esseva constatabile. Pericardectomia e valvulotomia tricuspide esseva executate simultaneemente. Le resultatos esseva bon.

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AN UNUSUAL CASE OF PULSUS ALTERNANS RECORDED DURING CARDIAC CATHETERIZATION FROM THE PULMONARY AND SYSTEMIC BLOOD VESSELS

PEDRO DE RABAGO, M.D.,* FRANZ W. KOHOUT, M.D., AND LOUIS N. KATZ, M.D.

CHICAGO, ILL.

INTRODUCTION

SINCE Traube first described pulsus alternans in 1872, it has been considered a sign of severe left-ventricular incompetence when present in organic heart disease. Usually it has a bad prognostic significance, and on occasion precedes other more familiar signs of heart failure and thus may be useful in predicting the appearance of the latter. Pulsus alternans that occurs at a slow heart rate is more significant than that at a faster rate, so that the slower the rate the more serious is the prognosis. However, alternation may also be present in non-diseased hearts and then is usually associated with tachycardia or arrhythmias, and in such cases is of no prognostic significance. Electrical alternans may occur with mechanical alternans or as an isolated entity and has the same clinical connotation as the latter.[13]

It is generally agreed that the weaker heart beats have a prolonged isometric contraction phase, a shortened ejection period, and a lengthened isometric relaxation phase, when compared to the stronger beats. The duration of systole is usually shorter in the weaker than in the larger beats,[10] though there are exceptions.[3] The left-ventricular pressure curve shows that, compared with normal, the weaker beats start at a lower, and the stronger beats at a higher, end-diastolic pressure.[10]

Three explanations have been offered as possible mechanisms for pulsus alternans: (a) alternating total hyposystole, in which it is assumed that the entire myocardium contracts but more feebly every alternate beat; (b) alternate partial hyposystole, in which it is assumed that the myocardium is dissociated functionally into separate contractile fractions, some of which contract poorly every other beat; (c) alternate partial asystole, in which it is assumed that certain parts of the myocardium fail to contract every other beat.

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

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*Fellow (from the University of Madrid, Madrid, Spain) of the Henry L. and Grace Doherty Charitable Foundation, Inc., New York City, N. Y.

It has been emphasized that hydrodynamic changes secondarily influence the pulsus alternans and contribute to its perpetuation.[3] The entire subject has been thoroughly reviewed previously.[1,3]

There have been many reports in the literature concerning mechanical alternans; most of them deal with alternation of the pulses in the systemic circuit. We have been able to find one reported case of pulsus alternans in man of the pulmonary arterial volume pulse recorded with the elektrokymograph;[6] this was associated with an intermittent pre-excitation (Wolff-Parkinson-White) syndrome. Another case (Case 5) is mentioned incidentally,[14] in which the pulsus alternans appeared during catheterization in the right ventricle, pulmonary artery, and wedge pressure in the pulmonary vein.

In the case we are reporting here, pulsus alternans was found in the pressure pulses of the left and right atria, in the pulmonary and jugular veins, in the pulmonary and femoral arteries, and in the right ventricle. In addition, it occurred in the coronary sinus and pulmonary venous wedge pressure curves. Such a wide distribution of mechanical alternans is unique in man. Because of this distribution, certain information could be derived concerning the mechanism of its perpetuation

CASE REPORT

J. K., a 2-year-old white male child, was born prematurely at 7 months. He was never cyanotic but was noted to have a "heart murmur." No definite diagnosis could be made at this time. The patient had been asymptomatic but his development, both mental and physical, had been deficient. There was no history of squatting. The mother had a questionable undiagnosed rash in the fourth month of gestation. Physical examination revealed a pale, noncyanotic, markedly underdeveloped child with some suggestion of mongoloid configuration. A systolic thrill was palpable over the pulmonic area, and a long Grade 3 to 4, rough systolic murmur was audible over the precordium with its maximum intensity between the second and third left intercostal spaces near the sternum. The second pulmonic sound was normal. The lungs were normal on examination. The liver was barely perceptible under the costal margin. No clubbing or edema was present. Fluoroscopically an enlarged right ventricle without dilatation of the right atrium was seen. The lung fields were clear.

Electrocardiogram: Rate 125; P-R interval, 0.16 sec.; and QRS, 0.12 sec. Sinus tachycardia. "Electrical horizontal" position. P-congenitale and right bundle branch system block were suggestive in congenital heart disease of a marked degree of right-heart strain.

Catheterization findings: In addition to the usual course of the catheter, it was possible to pass it from the right atrium into an anomalous left superior vena cava and then into the left jugular vein. Also from the right atrium it was possible to go through an interatrial septal defect into the left atrium, and from there into the pulmonic vein, and to get a wedge pressure curve (PAC) reflecting the pulmonary arterial pressure. The oxygen content of the blood samples showed the existence of a left-to-right shunt, and it would appear from the arterial saturation that there may have been, in addition, a small right-to-left shunt.

DISCUSSION OF RESULTS

The typical findings in the pressure pulses are shown in Figs. 1 to 9. The presence of mechanical alternans in all of these pressure curves is obvious. This was not associated with any electrical alternans. Since both the right ventricular pressure curve and the pulmonary arterial pressure curve, as well as the femoral arterial pressure curve, showed alternately large and small beats, it is

Fig. 1.

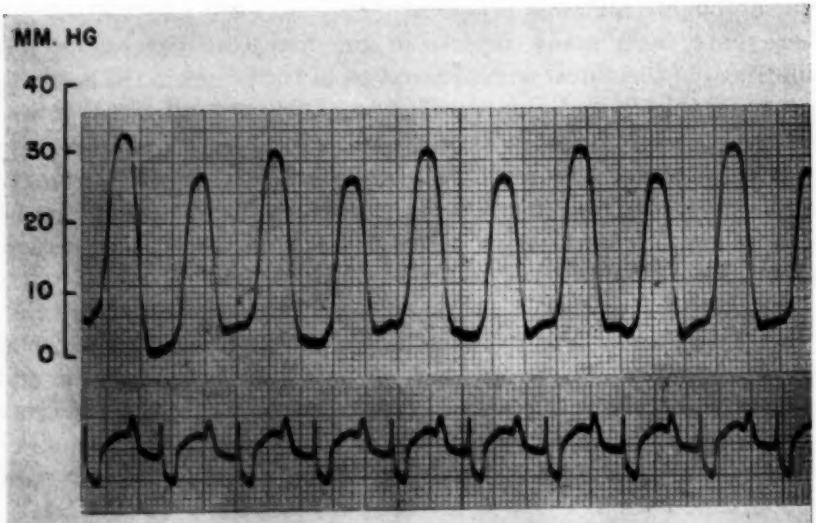
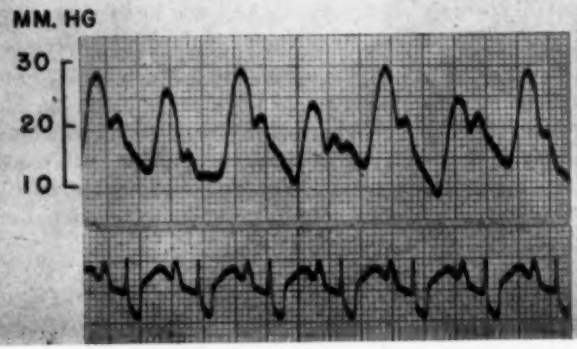


Fig. 2.

Fig. 3.



Figs. 1, 2, 3. *(For legends see opposite page.)*

obvious that this alternans involved both the right and left ventricles. Likewise there was alternans in both atria. Since simultaneous pressures were not recorded from the right and left sides of the heart, or its entering or exit vessels, we are not able to prove with certainty whether the alternation occurred concordantly or discordantly in both ventricles, that is whether the alternans was in or out of phase on the two sides of the heart. However, certain information is strongly suggestive that the alternans was, so to speak, out of phase, and this lends support to the idea that the alternation was primary in the right ventricle in which a conduction defect was present.

The evidence for the view that the alternans is out of phase in the two ventricles is as follows:

The taller beats in the right ventricle follow the higher end-diastolic pressure (Fig. 1), and this would be in accord with the adjustment of the heart to its filling. This alternation in the size of the right ventricular contraction would lead to the alternation of the pressure pulse in the pulmonary artery (Fig. 2), and in the pulmonary venous wedge pressure (Fig. 3) which is a reflection of the peripheral pulmonary arterial pressure. Furthermore, the larger A wave in the jugular pulse (Fig. 6) would be expected to precede the larger beat in the right ventricle and so would precede the larger beat of the pulmonary artery.

Now, if the two ventricles had their alternans out of phase, the small beat in the systemic arteries, including the femoral (Fig. 9), would occur simultaneously with the large beat in the pulmonary arteries, that is at a time just after the large A wave in the jugular pulse. Conditions would be reversed as far as the size of the systemic arterial beat following the small A wave in the jugular pulse. The transmission of such a systemic arterial pulse to the systemic venous system, either directly through the walls or via the systemic capillaries would result in a large arterial impact wave in the latter after the small A wave and a small arterial impact wave after the large A wave. That is exactly what occurs in the jugular pulse contour (Fig. 6).

Fig. 1.—Alternation of right ventricular pressure curves. Pressure pulse above; electrocardiogram, Lead II, below. Calibration on left. The larger beats start at higher end-diastolic pressure (5 mm. Hg) than the weaker beats (3 mm. Hg). The maximum systolic pressures are, respectively, 33 and 28 mm. Hg. The Q-V interval (from the beginning of Q to the onset of the pressure rise in the ventricle) equals 0.06 sec. Discussed in text.

Fig. 2.—Alternation of the main pulmonary arterial pressure curve arranged as in Fig. 1. The diastolic pressure following the weaker beat is 15 mm. Hg, while that following the larger beats is lower, 10 mm. Hg. The dicrotic wave is more marked in the weaker than in the stronger beats. Maximum systolic pressures are 30 and 25 mm. Hg, respectively, for the larger and smaller beats. The Q-P interval from the beginning of Q to the onset of the pressure rise in the pulmonary artery equals 0.12 sec. Q-V interval minus Q-P interval, the isometric contraction period of the right ventricle, equals 0.06 sec. (0.12 sec. minus 0.06 sec.). The normal isometric contraction period of the right ventricle equals 0.02 to 0.04 sec. Discussed in text.

Fig. 3.—Alternation in the pulmonary venous wedge pressure arranged as in Fig. 1. The pressure pulse is smoother than that in the pulmonary artery (Fig. 2). In the larger beats the maximum systolic and the following diastolic pressures are, respectively, 29 and 9 mm. Hg, while in the smaller beats these values are 25 and 13 mm. Hg, respectively. Q-P interval (see Fig. 2) equals 0.16 sec. Transmission time from pulmonary artery to pulmonary arterial capillary therefore equals 0.04 sec. (the difference between the Q-P interval of the main pulmonary artery and that of the pulmonary arterial capillary). Discussed in text.

Fig. 4.

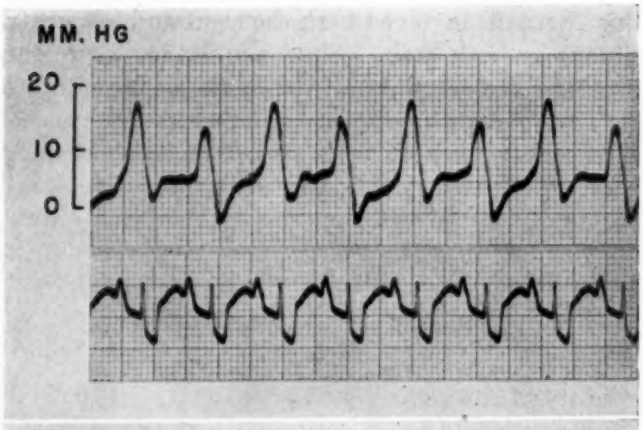


Fig. 5.

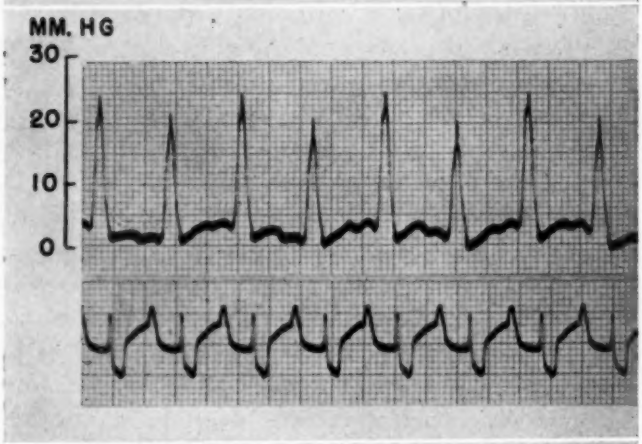


Fig. 6.

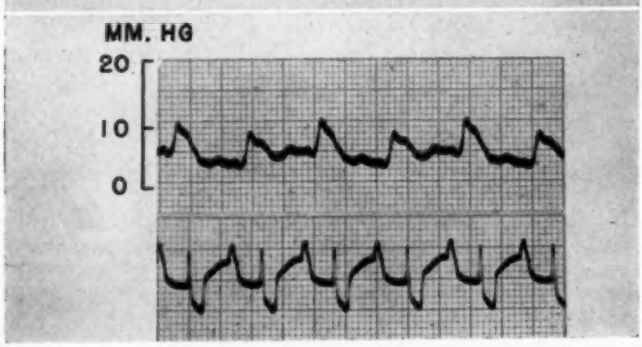


Fig. 4.—Alternation in the right-atrial pressure pulse. Arranged as in Fig. 1. The larger A wave has a maximum pressure of 17 mm. Hg, compared with 13 mm. for the smaller A waves. The pressure dip at the end of the large A wave reached 2 mm. Hg compared with −3 mm. for that after the smaller A wave. Q-A interval (from the beginning of Q to the peak of the A wave) equals 0.38 sec. Discussed in text.

Fig. 5.—Alternation in the coronary sinus pressure pulse arranged as in Fig. 1. This pattern is a distorted reflection of the right-atrial pressure pulse. Large A waves have a maximum systolic pressure of 25 mm. Hg compared with 21 mm. in the smaller waves. The pressure at the end of the large A wave is 2 mm., that at the end of the small wave 1 mm. Hg. Q-A waves, measured as in Fig. 4, equal 0.38 sec. Discussed in text.

Fig. 6.—Alternation in left jugular venous pressure pulse (which drains through an anomalous left superior vena cava into the coronary sinus). Arranged as in Fig. 1. The larger A waves have a maximum pressure of 11 mm. Hg compared to 9 mm. in the smaller A waves. The pressure at the end of the large pulse equals 4 mm. Hg, at the end of the small pulse equals 6 mm. Q-A interval, measured as in Fig. 4, equals 0.39 sec. Discussed in text.

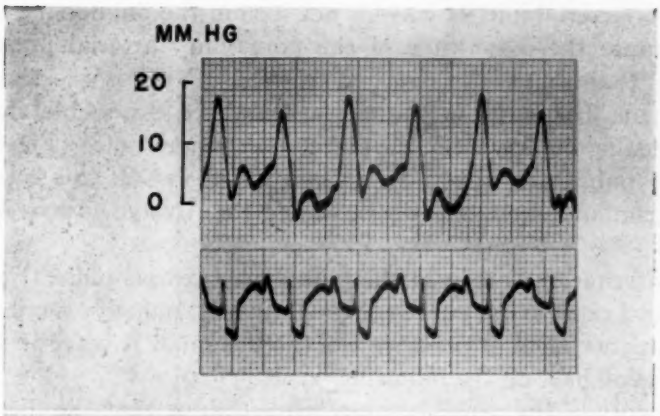


Fig. 7.

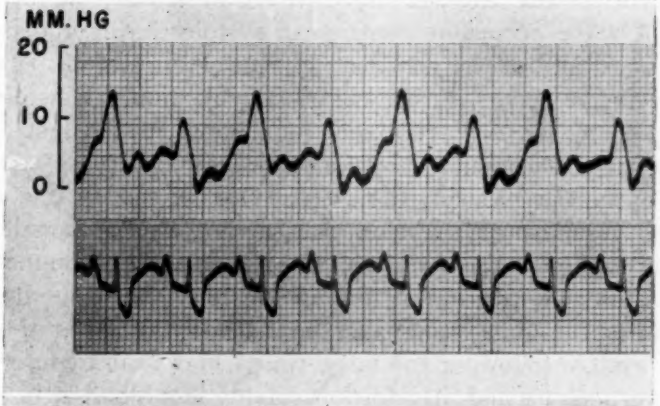


Fig. 8.

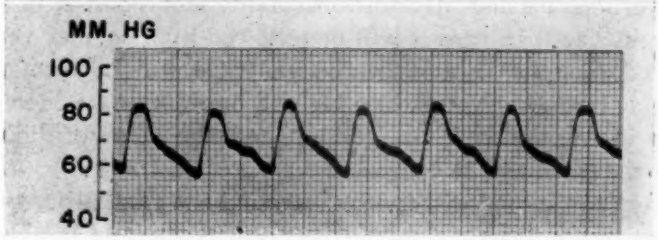


Fig. 9.

Fig. 7.—Alternation in the left-atrial pressure pulse. Arranged as in Fig. 1. The larger A wave has a pressure of 18 mm. Hg, while that of the smaller A wave is 15 mm. The pressure dip after the larger A wave reaches 3 mm. Hg, after the smaller A waves, −3 mm. The Q-A interval, measured as in Fig. 4, equals 0.38 sec. Discussed in text.

Fig. 8.—Alternation in pulmonary vein pressure pulses. Arranged as in Fig. 1. The larger A wave has a maximum pressure of 15 mm. Hg, that of the small A wave, 10 mm. The dip at the end of the A wave reaches 3 mm. after the large and 1 mm. after the small A wave. Note the small wave, which comes just before the A waves, is larger before the larger A wave than before the smaller one. The Q-A interval, measured as in Fig. 4, equals 0.42 sec. The transmission time of the A-wave peak from the left atrium to the pulmonary vein is equal to 0.04 sec. (the difference between this measurement here and in the left atrium). Discussed in text.

Fig. 9.—Alternation of the femoral arterial pressure pulse. The pressure in this figure is recorded at two-fifths the sensitivity of the pressure pulses in Figs. 1 to 8. The maximum pressures are, respectively, 86 and 83 mm. Hg for the larger and smaller pulses. The diastolic pressure is 59 mm. Hg after the large and 61 mm. after the small pulse beat. Discussed in text.

This kind of arterial impact wave is not seen in the pulmonary venous pulse, apparently because the magnitude of the pulmonary arterial pressure pulse is so much smaller than that of the systemic arteries. Perhaps it is counterbalanced by another factor, the surge in the left atrium. It is possible that the small wave just preceeding the A wave in the pulmonary venous pulse (Fig 8) is all that remains of the pulmonary arterial transmitted wave. If this is so, then there is the same discordancy between this wave and the A wave as seen in the jugular pulse.

Another alternation is seen in the pulmonary venous pulse (Fig. 8), as well as in the left and right atrial curves (Figs. 7 and 4), namely, the large A wave is followed by a higher level of pressure than is the small A wave in the alternant beat. This is explained on the following basis.

Measurements of the atrial pressure curves show that the dip immediately following the A wave occurs in ventricular systole during the isometric contraction phase, and all but the very last portion of the stretch between this dip and the next A wave occurs during ventricular ejection. Diastole of the ventricles is occupied by the A wave except for a short stretch just before it.

Now, the larger ventricular beat empties the heart more completely than the smaller one, thereby reducing the systolic residue and, in this way, lowering the diastolic ventricular pressure below that existing after the smaller ventricular beat. Since on each side the atrium and ventricle form a common chamber in ventricular diastole, the pressure in the atrium (and the veins draining into it) will also fall after the large ventricular beat below that after the smaller one. The auricular systole following the large ventricular beat therefore will have a lower maximum pressure and, in addition, having less blood in it when it starts, will be smaller in size. In turn it will be followed by a smaller ventricular beat because the end-diastolic volume of the ventricle will be smaller. After the small ventricular beat the systolic residue will once again be increased, the diastolic pressure in the ventricle, its atrium, and the veins draining into it will be higher, and the cycle will be complete.

In this way the "surge" will continue around the circulatory tree, discordant in the two sides of the heart, as pointed out previously, and having a periodicity equal to just one-half the heart rate. This discordancy is a mechanism which tends to perpetuate the alternation (cf. Fig. 10). The A-V valve vibrations and A-V junction movement play a minor role apparently in the atria compared to this dynamic surge.

This effect would dominate in the venous pulse if the transmitted arterial impact wave is small, as is the case in the pulmonary veins (Fig. 8). When, however, the transmitted pressure impact wave from the arteries is large, the latter obscures this phenomenon as is the case in the jugular pulse (Fig. 6). In this way the discordancy is explained in the alternation in pressures occurring between A waves of the right atrium and jugular veins. Only in the latter does the arterial impact wave dominate.

The coronary sinus pulse (Fig. 5) is a distortion of that in the right atrium, as is to be expected in view of previous work from this department.[12] It shows the expected alternans.

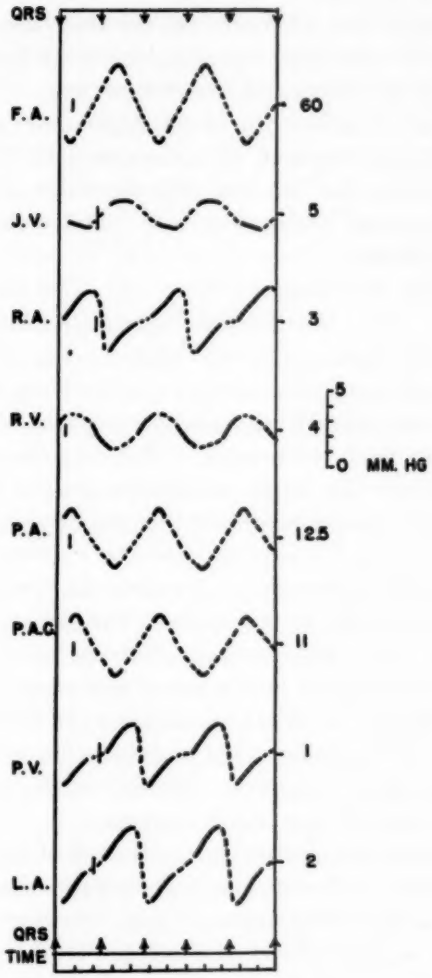


Fig. 10.—A diagram showing the periodic surge, over 5 heart cycles, of the pressure in the several parts of the circulation after omitting the superimposed pressure waves imparted by atrial and ventricular contraction. Zero time is the onset of the first QRS complex. In constructing these curves the minimal diastolic pressures of the arteries and the diastolic portions of the other part of the circulatory tree, excluding the superimposed waves, were used. The solid parts of the curves are actual pressures, the dotted portions are drawn in between. The onset of the next five QRS complexes are indicated at the top and bottom at the levels marked QRS. Time below in 0.2 sec. The height of the pressure scale at the right is 5 mm. Hg, divided into millimeters. Mean pressure (in mm. Hg) of each constructed curve is given by the values on the right. A vertical mark at the right of the zero line shows the onset of the first systolic rise of pressure in the case of the ventricle and arteries, and the peak of the first A wave in the case of the veins and atria. *F. A.* is femoral artery; *J. V.*, jugular vein; *R. A.*) right atrium; *R. V.*, right ventricle; *P. A.*, pulmonary artery; *P. A. C.* ("pulmonary arterial capillary") is a wedge pressure in the pulmonary vein reflecting pulmonary arterial pressure; *P. V.*, pulmonary vein; *L. A.*, left atrium.

Ordinarily the larger beat in an alternans, at least in the systemic circuit, has the longer duration of systole, so that diastole is encroached upon more, and less time is available for diastolic run-off into the capillaries. The net result is that the diastolic pressure following the large beat is higher than that following the smaller beat where the reverse occurs. This was not the case here in the femoral arterial pulse, nor in the pulmonary arterial pulse (central or peripheral). The unusual type of alternans seen in this case in the arterial pressure pulses consisted in the fact that the diastolic pressure after the larger beat was lower than that after the smaller one. This was particularly marked in the pulmonary arterial pulses.

Three facts probably contribute to this: (1) The absence of alternation in the duration of diastole. (2) The possible appearance late in diastole—actually almost in presystole—of large reflected waves. On this assumption, being reflected from the terminus of the arterial system they have a change in sign so that they appear as negative waves which summate with the late portion of the oncoming wave and lead to a drop in the diastolic pressure level. Since the larger beat would have the larger negative reflected wave following it, this diastolic drop in pressure would be greater in the large than in the small beat. (3) The greater opportunity for run-off into the capillaries in the larger than in the smaller beat which comes about because the pressure gradient between the arterial and venous system at the time of the larger beat is bigger than at the time of the smaller one. This is so not only because of the higher pressure in the artery (and the associated larger cross section of the terminal bed), but because the venous pressure at this time is lower as discussed previously.

Thus, in this case the periodic surge of pressure occurring every other beat sweeps through the circulatory system. Its ebb in the pulmonary circuit coincides with the surge in the systemic and vice versa.

Since the Q-A interval (as defined in the legend of Fig. 4) is the same in the right and the left atrium, 0.38 sec., one can assume that systole in both atria occurs simultaneously. The transmission time between the several chambers for homologous points is pointed out in the legends of the figures, and the protracted duration of the isometric contraction period in the right ventricle in this case, associated with a right bundle branch system block, is noted.

The presence of the right bundle branch system block fortifies the conclusion that the alternans is primarily initiated in the right ventricle from time to time, probably by respiratory disturbances or heart irregularity in the form of premature beats. The presence of alternans in the other chambers of the heart probably stems from the alternating variations in hydraulics which this right ventricular alternans precipitates. As previously pointed out by one of us in another connection[3] the importance of alternating hydrodynamics in perpetuating mechanical alternans is supported by this case.

The ability to study so many portions of the systemic and pulmonary circuit in rapid succession is of value, as this case shows, in arriving at the intricate interrelationships that initiate and sustain mechanical alternans. More information along these lines might give greater insight into the multiple problems of the hydrodynamics involved, and if opportunity arises to record simultaneous pressure from the two sides of the circulation, more insight would be obtained.

The patient had a left-to-right shunt, and probably a less significant right-to-left one, as revealed by the catheterization data. If the alternans is out of phase in the left and right sides of the heart, as the analysis of the data leads us to conclude, then the left-to-right shunt would be more significant during the larger systoles of the left atrium which correspond to the weaker systole of the right atrium. During the larger beats in the right atrium, corresponding to the weaker beats of the left atrium, the pressure gradient would be reversed, and the shunt would be primarily right-to-left, but smaller than the left-to-right one. If this argument is true, this case would have an alternation, the first described in the literature, of right-to-left and left-to-right interatrial shunting.

CONCLUSIONS

1. Alternation of pressure pulses in the lesser circuit in a case of congenital heart disease is reported. This is, as far as we know, the first one so extensively studied in man. This case also showed an alternans in the pulmonary circuit apparently discordant to that in the systemic circuit. This caused a surge of pressure to sweep around the circulatory tree, with a period equal to one-half the heart rate. Evidence is presented to suggest an alternating reversal of the interatrial shunt.

2. The alternans was constant, independent of respiration and not accompanied by electrical alternans. It was present to a greater or lesser extent in all the pressure curves obtained during catheterization, namely, right ventricle, both atria, coronary sinus, jugular vein, pulmonary arteries and veins, pulmonary venous wedge pressure, and femoral artery. It was unrelated to a persistent change in cardiac rhythm and was not accompanied by measurable differences in the duration of systole and diastole between the large and small beats.

3. Contrary to previous reports, the higher diastolic pressures in the main vessels leaving the heart follow the beats with lower systolic pressures. The isometric contraction period of the right ventricle is prolonged to 0.06 sec. associated with the presence of a right bundle branch system block.

CONCLUSIONES IN INTERLINGUA

1. Es reportate un caso de congenite morbo cardiac con mechanic pulsos alternante—apparentemente in discordo mutual—in le circulation e pulmonar e systolic. Le extraordinarimente extense occurrentia de pulso alternante in iste caso offereva un opportunitate unic pro colliger datos significative in re le mechanismo de su perpetuation.

2. Le pulso alternante esseva constante, independente del respiration, e non accompaniate per alternation electric. Illo esseva presente plus o minus pronunciatemente in omne le curvas de pression obtenite durante catheterisation. Illo monstrava nulle relation con un persistente cambiamento de rhythmo cardiac e non esseva accompaniate per cambiamentos mesurabile in le duration de systole e diastole inter le pulso major e minor.

3. In contrasto con previe reportos, le altiate pressiones diastolic in le vasculos major exiente ab le corde occurreva post le pulsos de basse pressiones systolic. Le periodo de contraction isometric del ventriculo dextere esseva prolongate a 0,06 sec, associate con un bloco de branca dextere.

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Book Reviews

DISEASES OF THE HEART AND ARTERIES. By George S. Herrmann, M.S., M.D., Ph.D., F.A.C.P. Ed. 4, 652 pages. St. Louis, 1952, The C. V. Mosby Company. Price, $12.50.

The appearance in a few short years of the fourth edition of this volume dealing with diseases of the heart and arteries speaks highly for its popularity. The present edition compares very favorably with the previous ones. In fact, it has been extended to include an all-important discussion of the embryology of the heart which is so valuable in the understanding of congenital defects which are now becoming increasingly amenable to surgical therapy. Also, the special techniques of phonocardiography, electrocardiography, electrokymography, tomography, and cardiac catheterization are dealt with in a realistic fashion.

In most respects, the text has been completely re-oriented to the rapid advances in our knowledge of diseases of the heart and arteries in a comprehensive and extremely readable manner. It is a volume that is crammed with information and knowledge, and it should be of the greatest help to every internist and cardiologist.

J. C.

THE DIGITAL CIRCULATION. By Milton Mendlowitz, 182 pages, 31 tables, 60 figures, New York, 1954, Grune Stratton, Inc.

In his preface, the author advances three principal reasons for the importance of digital circulation as a justification for his book: (1) Digital circulation may reflect changes in the systemic circulation as a whole; (2) circulatory changes are often most pronounced, and therefore detectable earlier, in the acral parts of the circulation (fingers and toes); and (3) digital circulation may be studied with comparatively simple, bloodless methods, applicable at the bedside. Impressive material is presented in the text to document these claims. In view of the absence of a review of the extensive information about the digital circulation accumulated in the past two to three decades (the bibliography lists 636 references), the book fills a gap in the medical literature.

The author has been active in this field since 1938, and much of the illustrative material refers to his work. Four short introductory chapters are devoted to anatomy, physiology, pharmacology, and pathology of digital circulation (pp. 1-36). This is followed by a thorough and critical discussion of the various methods used (pp. 38-91). The changes of digital circulation in various circulatory diseases, in anemia and in polycythemia, are discussed in the last chapters (pp. 92-146).

This is a fluid, lucid and, at the same time, critical presentation of a comparatively recent field of circulatory research, profusely illustrated with tables and figures. Undoubtedly, the book will stimulate further exploration in this area and clinical application.

E. S.

SPATIAL VECTORCARDIOGRAPHY. By George E. Burch, M.D., FACP, J. H. Abildskov, M.D., and J. A. Cronvich, M.S. Ed. 1, 173 pages. Philadelphia, 1953, Lea & Febiger, Price $5.00.

The authors, in response to many requests, have reproduced, in book form, their favorably received 1952 AMA exhibit on Spatial Vectorcardiography. They have made minor additions to and some changes in the text to elucidate a complicated subject and make it more easily understandable. The profusion of black and white drawings helps the beginner to visualize the basic concepts of the subject of vectorcardiography. The plotting of the instantaneous electrical axes from simultaneously taken multilead electrocardiograms might well have been given more consideration. The tracing of the vectors, reference frames, spatial relations of electrocardiography in vectorcardiography, and discussions of electrocardiograms in specific conditions have

been touched upon. The simplicity and brevity of presentation, as the authors point out, require slow and careful study in order to comprehend all the implications intended. Some more extensive discussions of concepts and methods would have been advantageous. The authors have chose the equilateral tetrahedron as the best spatial reference frame, as Dr. Frank N. Wilson and associates, especially Dr. Franklin Johnson, originally pointed out. They presume that any disadvantages in this system are the same as those of any other spatial reference frame that may be applied to the human body. Each system has its advocates and this multiplicity of methods will obscure the field until some generally acceptable standardization of reference frames, electrode positions, and nomenclature is established.

The authors have concentrated on the frontal and sagittal plane vector loops and have neglected to some extent the vector loops recorded in the transverse plane. In the hands of some investigators, the transverse loops have shown good correlation to the standard normal and abnormal electrocardiograms. The transverse plane when used occasionally by the authors warrants more attention to explanation which is necessary to prevent confusion. Vector loops offer some help in visualization of electrocardiography. The authors agree that vectorcardiography is still in the experimental stage and that vectorcardiograms constructed from ordinary routine electrocardiograms are likely to be erroneous. Vectorcardiographic loops, right ventricular hypertrophy, and right bundle branch block, especially the incomplete type and similar left-sided manifestations, really call for more extensive treatment than has been accorded.

This monograph is a well organized presentation of results of the authors' investigations of a difficult subject. The text is concise and brief so that the internist can get a fairly satisfactory concept of the subject of vectorcardiography. The possible supplemental value in the elucidation of electrocardiographic tracings is just broached and would seem to warrant more extensive treatment. The beginner in vectorcardiography should read this book first.

G. R. H

Author's Revision and Addendum

In the review, "Theory of Vectorcardiography: A Review of Fundamental Concepts" which appeared in the Am. Heart J. 49:135, 1955, the following three corrections should be made:

1. Delete lines 22 through 31 on page 148. Substitute for this deletion the following: (3) The vectors of leads (V_{P1}–V_T) and (V_{P2}–V_T) lie along a single electrical axis. In accordance with recent studies of Frank[54] the single resultant dipole representing the heart need not be located on this axis for perfect cancellation to occur. This fact, which the reviewer recognizes as being unquestionably established, is contrary to the conclusion drawn in the papers of Schmitt and his associates[31-33] that excellence of cancellation is partially dependent upon electrical neutrality of the Wilson central terminal.

2. Delete paragraph consisting of lines 43 through 46 on page 150 and lines 1 through 4 on page 151.

3. Delete parenthetical phrase consisting of lines 12 through 14 on page 152.

Add the following reference:

54. Frank, E.: Measurement and Significance of Cancellation Potentials on the Human Subject, Circulation (To be published).